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BIOLOGICAL PRODUCTS

APRIL 1978 - MARCH 1980

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

HE 20. 4006/2:

ACKNOWLEDGMENT

This publication was prepared under the overall direction of Agnes B. Black, Federal Register Writer, Food and Drug Administration, and the finished product reflects many diligent hours of preparation, review, and quality control by Lola Batson, Marcia Rosenburg, and other members of the FRW staff.

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FOREWORD

All narrative preambles for this cumulative pocket supplement have been compiled from published FEDERAL REGISTER documents relating to the Biological Products Regulations of the Food and Drug Administration, from April 1978 through March 1980.

Arranged to parallel the subject matter organization of Title 21 of the Code of Federal Regulations, this supplement is part of a comprehensive effort to make available to the public and the agency a central source for tracing the historical development of agency regulations by subject.

An agency User Review Committee conducts a technical oversight review of each volume and provides a potential user perspective to the decisionmaking process.

This cumulative pocket supplement to the original volume will be updated annually corresponding to the April 1 revision date of 21 CFR Chapter I. Notice of the availability of original volumes and pocket supplements will be published in the FEDERAL REGISTER upon printing.

JERE E. GOYAN
Commissioner of Food and Drugs

HOW TO USE THIS BOOK

The preamble compilation series is structured to follow the current organizational scheme for Food and Drug Administration regulations. It includes published final regulations, published proposals including proposals awaiting final action, significant proposals and final regulations that have subsequently been revoked, and substantive notice documents that relate to subsequent regulatory actions or certain statements of agency policy.

Certain classes of rule documents are excluded, including delegations of authority, organization statements, and fee documents.

Certain classes of "routine" documents are excluded. These are documents related to individual NADA's; food additives; GRAS affirmations; medical device classifications, standards, and premarket approvals; color additives; advisory committees; and antibiotic regulations. However, selected, major actions in these classes are included.

The outline and numbering system used in the preamble compilation is designed to establish an interrelationship between the original compilation and pocket supplements and has no relevance to the numbering systems used in the CFR; however, in most cases, the major subject groupings in the compilation parallel part designations in the CFR.

Documents appearing in the cumulative supplement are indicated with a dagger (†) in the revised table of contents for the supplement. All finding aids appearing in the supplement have been updated to include material in the original volume and the supplement.

This compilation reflects the correction of errors appearing in the original FEDERAL REGISTER publication. Page numbers have been inserted in the text to maintain the FEDERAL REGISTER page relationship to permit comparison between the compilation and original publication. No substantive changes have been made in any document; however, the original documents filed with the office of the FEDERAL REGISTER, rather than the published version of the document, represents the original source material for the compilation.

Any document pertinent to more than one subject area is marked with an asterisk (*) in the table of contents and appears in its entirety under each subject in the compilation series for the convenience of the reader.

READEX FICHE

Table of Contents

	Page
Foreword	iii
How to Use This Book	v
I. General	
A. General Provisions	2
3.— Advertising	2
3.1 Notice	2
20.— Biological Drugs Containing Antibiotics	2
20.1 Final Regulation	2
50.— Clarifying and Conforming Amendments	3
50.1 Proposal	3
50.2 Final Regulation	3
50.3 Final Regulation	4
B. Administrative Procedures	6
†5.— Adverse Reactions and Product Experiences	567
†5.1 Availability of Draft Proposal	567
15.— Dating Periods and Proper Names	6
15.1 Proposal	6
15.2 Final Regulation	7
15.3 Proposal	7
15.4 Final Regulation	8
15.5 Proposal	8
15.6 Final Regulation	8
15.7 Proposal	9
15.8 Final Regulation	9
15.9 Final Regulation	10
15.10 Final Regulation	10
15.11 Final Regulation	11
†15.12 Proposal	568
*17.— Public Disclosure of Specifications for Biological Products	12
17.1 Proposal	12
*18.— Public Information; Disclosure of Existence	15

Page

18.1 Proposal 15
†18.2 Extension of Time for Comments 569
20.— Records and Record Retention 22
20.1 Proposal 22
20.2 Final Regulation 23
25.— Samples 23
25.1 Final Regulation 23
30.— Shipping Temperatures 24
30.1 Proposal 24
30.2 Final Regulation 24
32.— Shipping Temperature of Frozen Red Blood Cells 25
32.1 Proposal 25
32.2 Final Regulation 25
35.— Shipping Temperature of Live Measles, Mumps, and Rubella Virus Vaccines 26
35.1 Proposal 26
35.2 Final Regulation 26
37.— Shipping of Whole Blood 28
37.1 Proposal 28
37.2 Final Regulation 28
45.— Storage Requirements for Measles, Mumps, and Rubella Virus Vaccines 28
45.1 Final Regulation 28
C. Tests and Methods 29
15.— Purity Standards 29
15.1 Proposal 29
15.2 Final Regulation 29
20.— Pyrogenic Substances 30
20.1 Proposal 30
20.2 Final Regulation 30
40.— General Safety Test 35
40.1 Proposal 35
40.2 Final Regulation 36
43.— Inactive Influenza Vaccine Safety Test 43
43.1 Proposal 43
43.2 Final Regulation 46
50.— Sterility Requirements 50
50.1 Proposal 50

Page

50.2 Final Regulation 51
†50.3 Final Regulation 570
52.— Sterility Standards for Blood Products 51
52.1 Final Regulation 51
52.2 Proposal 52
54.— Sterility Test and Use of Spore-Bearing Organisms 52
54.1 Proposal 52
54.2 Final Regulation 53
54.3 Final Regulation 53
57.— Sterility Testing; Alternative Thioglycollate Medium 53
57.1 Proposal 53
57.2 Final Regulation 54
†60.— Sterility; Membrane Filtration 570
†60.1 Final Regulation 570
E. Efficacy Review 56
3.— General Procedures 56
3.1 Proposal 56
3.2 Final Regulation 57
†3.3 Final Regulation 571

II. Labeling Statements and Requirements

B. Blood and Blood Products 63
7.— Donor Labeling 63
7.1 Proposal 63
7.2 Proposal 69
7.3 Final Regulation 77

III. Licensing, Listing, and Registration

B. Registration and Listings 88
3.— Registration of Blood Banks 88
3.1 Proposal 88
3.2 Final Regulation 89
3.3 Final Regulation 93

IV. Good Manufacturing Practices

A. General 95
1.— Whole Blood, Red Blood Cells and Allergenic Products 95
1.1 Proposal 95

Page

1.2 Final Regulation 95

B. Good Manufacturing Practice for Blood and Blood Components 96

3.— Blood and Blood Components 96

3.1 Proposal 96

3.2 Final Regulation 100

3.3 Proposal 119

† 3.4 Withdrawal of Proposal 572

†5.— Calibration of Hematocrit Centrifuges and Vacuum Blood Agitators 573

†5.1 Proposal 573

†5.2 Final Regulation 574

V. Biologics for Investigational Use

3.— General Procedures 121

3.1 Final Regulation 121

15.— Licensing Requirements for Controlled Investigations 121

15.1 Final Regulation 121

VIII. Bacterial Products

A. General 122

5.— Efficacy Review 122

5.1 Proposal 122

5.2 Opportunity for Hearing on Intent to Revoke Licenses 231

† 5.3 Final Regulation 576

B. Tests and Methods 233

45.— Pertussis Vaccine Safety Test 233

45.1 Final Regulation 233

D. Specific Additional Standards for Bacterial Products 234

5.— Anthrax Vaccine, Adsorbed 234

5.1 Proposal 234

5.2 Final Regulation 234

10.— Cholera Vaccine 235

10.1 Proposal 235

10.2 Final Regulation 236

10.3 Final Regulation 241

20.— Pertussis Vaccine 242

20.1 Proposal 242

Page

20.2 Final Regulation 242
30.— Typhoid Vaccine 243
30.1 Proposal 243
30.2 Final Regulation 243
†30.3 Proposal 585

IX. Viral Vaccines

A. General Provisions 245
5.— Containers 245
5.1 Proposal 245
5.2 Final Regulation 246
10.— Unavoidable Bacteriophage 246
10.1 Final Regulation 246
B. Tests and Methods 248
10.— Live, Attenuated Canine Renal Tissue Cultures 248
10.1 Proposal 248
10.2 Final Regulation 248
10.3 Final Regulation 248
25.— Monkey Kidney Tissue Culture 249
25.1 Proposal 249
25.2 Final Regulation 250
40.— Measles, Mumps, and Rubella Vaccine Neurovirulence Safety Tests 251
40.1 Proposal 251
40.2 Final Regulation 251
45.— Live Rubella Virus Vaccine Safety Test 253
45.1 Final Regulation 253
50.— Poliovirus Vaccine Safety Test 254
50.1 Final Regulation 254
65.— Smallpox Vaccine and Measles-Smallpox Vaccine Potency and Safety Testing 255
65.1 Proposal 255
65.2 Final Regulation 256
D. Specific Additional Standards for Viral Vaccines 259
5.— Adenovirus Vaccine 259
5.1 Proposal 259
5.2 Final Regulation 259
5.3 Notice of Opportunity for Hearing 260

Page

10.— Bacillus of Calmette and Guerin (BCG) Vaccine ... 261
10.1 Proposal ... 261
† 10.2 Final Regulation ... 587
25.— Measles Virus Vaccine, Live, Attenuated ... 262
25.1 Proposal ... 262
25.2 Final Regulation ... 262
28.— Measles-Smallpox Vaccine, Live ... 263
28.1 Proposal ... 263
28.2 Final Regulation ... 263
28.3 Proposal ... 263
28.4 Final Regulation ... 265
35.— Mumps Virus Vaccine, Live ... 266
35.1 Proposal ... 266
35.2 Final Regulation ... 266
† 35.3 Notice ... 596
40.— Poliomyelitis Vaccine ... 267
40.1 Proposal ... 267
40.2 Final Regulation ... 267
40.3 Proposal ... 268
40.4 Final Regulation ... 268
40.5 Final Regulation ... 269
40.6 Proposal ... 269
40.7 Final Regulation ... 269
40.8 Proposal ... 270
40.9 Extension of Time for Filing Comments ... 270
40.10 Proposal ... 270
40.11 Final Regulation ... 271
45.— Poliovirus Vaccine, Live, Oral ... 271
45.1 Proposal ... 271
45.2 Final Regulation ... 272
45.3 Proposal ... 272
45.4 Final Regulation ... 273
45.5 Proposal ... 273
45.6 Final Regulation ... 274
45.7 Proposal ... 274
45.8 Final Regulation ... 275
55.— Rubella Virus Vaccine, Live ... 275
55.1 Proposal ... 275
55.2 Final Regulation ... 276

Page

55.3 Proposal 276
55.4 Final Regulation 277
60.— Smallpox Vaccine 277
60.1 Proposal 277
60.2 Proposal 277
60.3 Final Regulation 278
60.4 Final Regulation 278

X. Human Blood and Blood Products

3. Tests and Methods 281
5.— Blood Grouping Serum 281
5.1 Proposal 281
5.2 Amended Proposal 282
5.3 Final Regulation 285
5.4 Extension of Effective Date 300
†5.5 Final Regulation; Correction 597
10.— Blood Group Substances A, B, and AB 300
10.1 Proposal 300
†10.2 Final Regulation 598
35.— Measles Antibody Titer of Globulin Products Replacement Reference 302
35.1 Final Regulation 302
41.— Hepatitis Associated (Australia) Antigens 303
41.1 Proposal 303
41.2 Final Regulation 304
41.3 Proposal 304
41.4 Final Regulation 307
42.— Hepatitis Associated (Anti-Australia) Antigen 314
42.1 Proposal 314
42.2 Final Regulation 314
42.3 Final Regulation 315
42.4 Final Regulation 315
43.— Hepatitis B Surface Antigen 316
43.1 Notice 316
43.2 Proposal 317
†43.3 Final Regulation 600
†43.4 Proposal 601
47.— Syphilis and Hepatitis B Surface Antigen Test 319
47.1 Final Regulation 319

Page

50.— Limulus Amebocyte Lysate 320
50.1 Notice 320
50.2 Proposal 321
50.3 Notice 322
†50.4 Proposal 603
65.— Leukocyte Typing Serum 324
65.1 Proposal 324
65.2 Final Regulation 325
75.— Reagent Red Blood Cells 330
75.1 Proposal 330
75.2 Final Regulation 332
C. Anticoagulants 339
15.— Citrate Phosphate 339
15.1 Proposal 339
†15.2 Final Regulation 606
†15.3 Proposal 609
D. Specific Additional Standards for Human Blood and Blood Products 342
5.— Whole Blood 342
5.1 Proposal 342
5.2 Final Regulation 342
5.3 Proposal 343
5.4 Final Regulation 343
5.5 Proposal 343
5.6 Proposal 344
5.7 Final Regulation 344
5.8 Amended Proposal 344
5.9 Final Regulation 345
5.10 Proposal 345
5.11 Final Regulation 346
5.12 Proposal 346
5.13 Final Regulation 347
5.14 Proposal 347
5.15 Final Regulation 348
10.— Red Blood Cells 348
10.1 Proposal 348
10.2 Extension of Time for Comments 349
10.3 Final Regulation 349
10.4 Final Regulation 350

Page

10.5 Final Regulation 350
15.— Platelet Concentrate 351
15.1 Proposal 351
15.2 Proposal 351
15.3 Final Regulation 353
15.4 Final Regulation 360
†15.5 Proposal 610
20.— Single Donor Plasma 362
20.1 Proposal 362
20.2 Final Regulation 364
30.— Cryoprecipitated Antihemophilic Factor 372
30.1 Proposal 372
30.2 Final Regulation 373
30.3 Proposal 373
30.4 Final Regulation 375
30.5 Final Regulation 381
35.— Source Plasma 382
35.1 Proposal 382
35.2 Final Regulation 383
35.3 Proposal 389
35.4 Notice to Manufacturers 394
35.5 Final Regulation 395
35.6 Extension of Effective Date 409
35.7 Proposal 410
35.8 Final Regulation 411
† 35.9 Notice of Availability of Guideline 613
†35.10 Proposal 614
40.— Normal Serum Albumin 413
40.1 Proposal 413
40.2 Proposal 414
40.3 Final Regulation 418
40.4 Extension of Effective Date 433
45.— Plasma Protein Fraction 434
45.1 Proposal 434
50.— Immune Serum Globulin 434
50.1 Proposal 434
50.2 Final Regulation 435
† 50.3 Notice of Availability of Guidelines 615

Page

55.— Measles Immune Globulin 435
55.1 Proposal 435
55.2 Proposal 436
55.3 Final Regulation 436

XI. Diagnostic Substances

A. General 437
*5.— In Vitro Diagnostic Products 437
5.1 Proposal 437
5.2 Final Regulation 439
5.3 Stay of Effective Date 444
5.4 Extension of Effective Date 445
B. Dermal Tests 445
10.— Cancer Testing In Vitro Diagnostic Biologic Substances 445
10.1 Notice to Manufacturers 445
20.— Diphtheria Toxin for Schick Test 446
20.1 Proposal 446
20.2 Final Regulation 447
†25.— Adsorbed Diphtheria and Tetanus Toxoids 616
†25.1 Notice of Availability of Guideline 616
40.— Tuberculin 447
40.1 Proposal 447
40.2 Final Regulation 448
40.3 Proposal 448
40.4 Final Regulation 449
40.5 Final Regulation 449

XII. Other Products

B. Allergenic Products 450
5.— Skin Test Antigen Efficacy Review 450
5.1 Proposal 450
†5.2 Final Regulation 617
10.— Allergenic Products 552
10.1 Proposal 552
10.2 Final Regulation 553
† 12.— Source Material for Allergenic Products 625
† 12.1 Proposal 625
† 12.2 Extension of Time for Comments 627
† 14.— Allergenic Product Multiple Dose Containers 628
† 14.1 Proposal 628

Page
†16.— Antigen E Potency Test..... 629
†16.1 Proposal..... 629
†16.2 Extension of Time for Comments 632
Redesignation Tables 555, 635

ALPHABETIC TABLE OF CONTENTS

	Page
†Adsorbed Diphtheria and Tetanus Toxoids	616
Adenovirus Vaccine	259
†Adverse Reactions and Product Experiences	567
Advertising	2
†Allergenic Product Multiple Dose Containers	628
Allergenic Products	450
Alternative Thioglycollate Medium; Sterility Test	53
Anthrax Vaccine, Adsorbed	234
†Antigen E Potency Test	629
Bacillus of Calmette and Guerin (BCG) Vaccine	261
Bacterial Products; Efficacy Review	122
Biological Drugs Containing Antibiotics	2
Biologics for Investigational Use	121
Blood Grouping Serum	281
Blood Group Substances A, B, and AB	300
†Calibration of Hematocrit Centrifuges and Vacuum Blood Agitators	573
Cancer Testing In Vitro Diagnostic Biologic Substances	445
Cholera Vaccine	235
Citrate Phosphate	339
Cryoprecipitated Antihemophilic Factor	372
Dating Periods	6
Diphtheria Toxin for Schick Test	446
Donor Labeling of Blood and Blood Products	63
Efficacy Review; General Provisions	56
General Safety Test	35
Good Manufacturing Practice for Blood and Blood Components	96
Hepatitis Associated (Anti-Australia) Antigen	314
Hepatitis Associated (Australia) Antigen	303
Hepatitis B Surface Antigen	316
Immune Serum Globulin	434
Inactive Influenza Vaccine Safety Test	43

	Page
In Vitro Diagnostic Products	437
Leukocyte Typing Serum	324
Licensing Requirements for Controlled Investigations	121
Limulus Amebocyte Lysate	320
Live, Attenuated Canine Renal Tissue Cultures	248
Live Rubella Virus Vaccine Safety Test	253
Measles Antibody Titer of Globulin Products Replacement Reference	302
Measles Immune Globulin	435
Measles, Mumps, and Rubella Vaccine Neurovirulence Safety Tests	251
Measles-Smallpox Vaccine, Live	263
Measles Virus Vaccine, Live, Attenuated	262
†Membrane Filtration, Sterility Test	570
Monkey Kidney Tissue Culture	249
Mumps Virus Vaccine, Live	266
Normal Serum Albumin	413
Pertussis Vaccine	242
Pertussis Vaccine Safety Test	233
Plasma Protein Fraction	434
Platelet Concentrate	350
Poliomyelitis Vaccine	267
Poliovirus Vaccine, Live, Oral	271
Poliovirus Vaccine Safety Test	254
Public Disclosure of Specifications for Biological Products	12
Public Information; Disclosure of Existence	15
Purity Standards	29
Pyrogenic Substances	30
Reagent Red Blood Cells	330
Records and Record Retention	22
Red Blood Cells	348
Registration of Blood Banks	88
Rubella Virus Vaccine, Live	275
Samples	23
Shipping of Whole Blood	28
Shipping Temperature of Frozen Red Blood Cells	25
Shipping Temperature of Live Measles, Mumps, and Rubella Virus Vaccines	26
Shipping Temperatures	24

	Page
ingle Donor Plasma	362
kin Test Antigen Efficacy Review	450
mallpox Vaccine	277
mallpox Vaccine and Measles-Smallpox Vaccine Potency and Safety Test	255
Source Material for Allergenic Products	625
ource Plasma	382
tandards for Whole Blood	342
terility Standards for Blood Products	51
terility Test and Use of Spore-Bearing Organisms	52
torage Requirements for Measles, Mumps, and Rubella Virus Vaccines	28
yphilis and Hepatitis B Surface Antigen Test	319
uberculin	447
yphoid Vaccine	243
navoidable Bacteriophage	246
iral Vaccine Containers	245
Whole Blood, Red Blood Cells and Allergenic Products	95

I. General

	Page
B. Administrative Procedures	6
†5.— Adverse Reactions and Product Experiences	567
†5.1 Availability of Draft Proposal—April 24, 1979 (44 FR 24233)	567
15.— Dating Periods and Proper Names	6
†15.12 Proposal—January 25, 1980 (45 FR 6120)	568
*18.—Public Information; Disclosure of Existence	15
†18.2 Extension of Time for Comments--May 30, 1978 (43 FR 23006)	569
C. Tests and Methods	29
50.—Sterility Requirements	50
†50.3 Final Regulation—March 2, 1979 (44 FR 11754)	570
†60.—Sterility; Membrane Filtration	570
†60.1 Final Regulation—October 13, 1978 (43 FR 47182)	570
E. Efficacy Review	56
3.—General Procedures	56
†3.3 Final Regulation—September 29, 1978 (43 FR 44838)	571

B. Administrative Procedures

†5.—Adverse Reactions and Product Experiences

†5.1 Availability of Draft Proposal—April 24, 1979

– 44 FR 24233 –

[Docket No. 79N-0089]

Biological Products; Adverse Reactions and Product Experiences; Availability of Draft Proposal

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) announces the availability of a draft of a proposed regulation requiring records and reports of adverse reactions and product experiences involving licensed biological products. Because of the potential impact this proposed regulation may have on the public and the regulated industry, FDA is making a draft of the proposed regulation available for public review and comment before publishing it as a proposal.

DATE: Comments by June 25, 1979.

ADDRESS: Written comments and requests for a copy of the draft of the proposed regulation to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Richard E. Fisher, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20205, 301-443-1306.

SUPPLEMENTARY INFORMATION: FDA is conducting a review of existing regulations governing biological products to ensure that the criteria for safety, purity potency, and effectiveness established by regulations are updated to reflect the most current scientific procedures necessary to protect the public health.

Consistent with this review, the agency will be proposing to amend the biologics regulations to define and prescribe specific procedures for all manufacturers of licensed biological products to follow in collecting and reporting information concerning adverse reactions (expected as well as unexpected), serious side effects resulting from the proper use or misuse of the product, manufacturing errors, product defects, and product failures. Adverse reactions and product experiences associated with blood and blood components would be exempt from compliance with the proposed regulation but are to be reported in accordance with existing Part 606 (21 CFR Part 606). The principal goal of the proposed regulation is to increase FDA's information base for effectively and efficiently regulating biological products. FDA will use this information to identify patterns, trends, frequency, seriousness, and significance of reactions for a continuing evaluation of a benefit/risk analysis for the product to determine whether additional label warnings, manufacturing changes, or investigations are needed, or whether new programs need to be initiated to ensure the continued availability of safe, pure, potent, and effective biological products.

Because of the potential impact this proposed regulation may have on the

public and the regulated industry, FDA is making a draft of the proposed regulation available for public review and comment before publishing it as a proposal. A copy of the draft is on public display in the office of the Hearing Clerk (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. In addition, copies of the draft of the proposed regulation are available from the Hearing Clerk; requests for copies should identify the Hearing Clerk docket number found in brackets in the heading of this document.

* * * * *

[FR Doc. 79-12746 Filed 4-23-79; 8:45 am]

15.—Dating Periods and Proper Names

†15.12 Proposal—January 25, 1980

– 45 FR 6120 –

[21 CFR Part 610]

[Docket No. 79N-0263]

Biological Products; Labeling Standards; Position and Prominence of Proper Name

AGENCY: Food and Drug Administration.

ACTION: Proposed Rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the general biological products standards regulation concerning the position and prominence of a manufacturer's logo in relation to the proper name of the product. This action is being taken following a reinterpretation of the regulation concerning the placement and prominence of the proper name of the product.

DATE: Comments by March 25, 1980.

ADDRESS: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Richard E. Fisher, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20205, 301-443-1306.

SUPPLEMENTARY INFORMATION: Section 610.62(a) (21 CFR 610.62(a)) of the biologics regulations requires that the proper name of the product on the package label be placed above any trademark or trade name used to identify the product and be symmetrically arranged with respect to other printing on the label. The prominence required for the proper name serves as a means of immediate recognition of a specific group or category of biological products and assures that all products in this category meet uniform criteria for safety, purity, and potency.

In interpreting and applying this regulation, FDA's Bureau of Biologics (Bureau) has in the past made no distinction between the terms "trade name" and "trademark." These terms were applied interchangeably by the Bureau and were not considered mutually exclusive.

However, the term "trademark," as defined in section 45 of the Trademark Act of 1946 (15 U.S.C. 1127) is separate and distinct from the definition and use of the term "trade name." A "trade name" is defined as the name used by a firm to identify its business when engaged in trade or commerce (15 U.S.C. 1127). A "trademark" is defined as any name, symbol, or device used by a firm to identify its goods and products and distinguish them from those manufactured or sold by others (15 U.S.C. 1127). The term "trademark" thus includes the name given to a product by a manufacturer and any logo used to identify the product.

In light of these statutory distinctions, FDA has reevaluated the purpose and intent of § 610.62(a) (21 CFR 610.62(a)), concerning the importance of a product's proper name and its required position and prominence of the package label. FDA concludes that a manufacturer's logo (symbol) may be placed above the proper name of a product, provided it is not more prominent than the proper name. However, all other aspects of the regulation remain unchanged.

Accordingly, FDA is amending § 610.62(a) to permit the placement of a manufacturer's logo above the proper name of the product consistent with other requirements contained in this section.

The agency has carefully considered the environmental effects of the proposed regulation and, because the proposed action will not significantly affect the quality of the environment, has concluded that an environmental impact statement is not required. A copy of the envionmental impact assessment is on file with the FDA Hearing Clerk.

Therefore, under provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 701, 52 Stat. 1040-1042 as amended, 52 Stat. 1050, 52 Stat. 1055-1056 as amended (21 U.S.C. 321, 352, 371)) and of the Public Health Service Act (sec 351, 58 Stat. 702 as amended (42 U.S.C. 262)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1), it is proposed that Part 610 be amended by revising § 610.62(a), to read as follows:

* * * * *

§ 610.62

* * * * *

[FR Doc. 80-2379 Filed 1-24-80; 8:45 am]

*18.—Public Information; Disclosure of Existence

† 18.2 Extension of Time for Comments—May 30, 1978

– 43 FR 23006 –

[21 CFR Parts 312, 314, 431, 514, 601, 807, 814]

[Docket No. 77N-0248]

PUBLIC INFORMATION

Disclosure of Existence; Extension of Comment Period

AGENCY: Food and Drug Administration.

ACTION: Proposed Rule: Extension of Comment Period.

SUMMARY: The comment period for the subject proposal is extended, based on a request for an extension, to provide additional time to submit comments.

DATE: Comments by June 30, 1978.

ADDRESS: Written comments to the Hearing Clerk (HFC-20), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Stuart M. Pape, Office of the General Counsel, Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4350.

SUPPLEMENTARY INFORMATION: In the FEDERAL REGISTER of March 28, 1978 (43 FR 12869), with a correction published in the FEDERAL REGISTER of March 31, 1978 (43 FR 13587), the Commissioner of Food and Drugs issued a proposal to amend existing regulations and promulgate new regulations to permit public disclosure of the existence and status of applications for approval of new drugs, new animal drugs, and medical devices pending before the Food and Drug Administration (FDA), and permit public acknowledgement of the existence of notices of intent to market medical devices. The proposal would further amend the agency's public information and related regulations to permit the agency to respond truthfully and accurately to inquiries about the existence of applications for investigational notices for new drugs, new animal drugs, and medical devices when those notices have been approved by FDA or allowed to become effective. Comments were to be submitted on or before May 30, 1978.

The Commissioner has received a letter from the German American Chamber of Commerce, Inc. (on file with the Hearing Clerk, address given above), requesting an extension of the comment period. The request asserts that additional time is necessary for the Chamber to obtain and evaluate comments from medical device manufacturers in Germany whom they represent and transmit the comments to FDA.

The Commissioner finds this request reasonable and extends the comment period to June 30, 1978.

* * * * *

Part 312

Part 314

Part 431

Part 514

Part 601

Part 807

Part 814

* * * * *

[FR Doc. 78-15191 Filed 5-26-78; 11:57 am]

C. Tests and Methods

50.—Sterility Requirements

† 50.3 Final Regulation—March 2, 1979

– 44 FR 11754 –

[Docket No. 79N-0005]

PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

Clarification of Bulk Sterility Test Requirements

AGENCY: Food and Drug Administration.

ACTION: Final Rule.

SUMMARY: This document amends the biologics regulations to clarify that only one repeat bulk sterility test is permitted in determining whether a lot of product meets the requirements for sterility.

EFFECTIVE DATE: March 2, 1979.

FOR FURTHER INFORMATION CONTACT:

Donna C. Williams, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20014, 301-443-1306.

SUPPLEMENTARY INFORMATION: The biologics regulation on sterility, § 610.12(b) (21 CFR 610.12(b)) provides that if growth appears in any of the test media during sterility testing of either bulk or final container material, the test may be repeated to rule out faulty test procedures. Section 610.12(b)(1) of the regulation further prescribes requirements for the bulk sterility tests while § 610.12(b) (2) and (3) prescribes requirements for the first and second repeat final container tests, respectively.

The intent of the regulation is to permit only one repeat bulk sterility test and two repeat final container tests. However, it has come to the attention of the agency that this regulation is occasionally misinterpreted to mean that more than one repeat bulk sterility test is permitted. To clarify the intent, § 610.12(b)(1) is amended to add a sentence to specify that only one repeat bulk test may be conducted.

Therefore, under the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)) and under authority delegated to the Commissioner (21 CFR 5.1), § 610.12 is amended by revising paragraph (b)(1) to read as follows:

* * * * *

§ 610.12

* * * * *

[FR Doc. 79-6224 Filed 3-1-79; 8:45 am]

† 60.—Sterility; Membrane Filtration

† 60.1 Final Regulation—October 13, 1978

– 43 FR 47182 –

[Docket No. 78N-0119]

PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

Sterility; Membrane Filtration; Amendment

AGENCY: Food and Drug Administration.

ACTION: Final Rule.

SUMMARY: This document amends a section of the biologics regulations by revising the reference to the United States Pharmacopeia (U.S.P.). This change is being made to ensure consistency with improvements in the sterility test by membrane filtration as prescribed in the U.S.P.

EFFECTIVE DATE: October 13, 1978.

FOR FURTHER INFORMATION CONTACT:

Iris Hyman, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20014, 301-443-1306.

SUPPLEMENTARY INFORMATION: The Bureau of Biologics is conducting a continuing review of the existing regulations governing biological products to assure that the criteria of safety, purity, potency, and effectiveness established by such regulations are updated to reflect current requirements for licensed products. Consistent with the review, the Commissioner is amending § 610.12(f) (21 CFR 610.12(f)) to change the reference to the membrane filtration test from the 18th Revision of the U.S.P., to the 19th Revision, in order to update a procedure which manufacturers are in fact already using.

Therefore, under the Public Health Service Act (sec. 351, 58 Stat. 702, as amended (42 U.S.C. 262)) and under authority delegated to the Commissioner (21 CFR 5.1), § 610.12 is amended in paragraph (f) by revising the first sentence, to read as follows:

* * * * *

§ 610.12

* * * * *

[FR Doc. 78-28573 Filed 10-12-78; 8:45 am]

E. Efficacy Review

3.—General Procedures

† 3.3 Final Regulation—September 29, 1978

– 43 FR 44838 –

[Docket No. 78N-0151]

PART 601—LICENSING

Amendment of Comment Period

AGENCY: Food and Drug Administration.

ACTION: Final Rule.

SUMMARY: This document amends a section of the biologics regulations to extend the time within which interested persons may submit comments on biological products review panel reports. This change is being made to provide interested persons with more time to review and to comment on the voluminous data and proposals contained in the panel reports.

EFFECTIVE DATE: September 29, 1978.

FOR FURTHER INFORMATION CONTACT:

Al Rothschild, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20014, 301-443-1306.

SUPPLEMENTARY INFORMATION: The biologics regulations, § 601.25(f)(4) (21 CFR 601.25(f)(4)), provide that any interested person may, within 60 days after publication of the proposed order in the FEDERAL REGISTER, file with the Hearing Clerk of the Food and Drug Administration written comments. The Commissioner is revising § 601.25(f)(4) to extend the comment period from 60 to 90 days to give interested persons more time to thoroughly review and comment on the proposed order as well as the panel report, which contains voluminous detailed data.

Therefore, under the Public Health Service Act (sec. 351, 58 Stat. 702, as amended (42 U.S.C. 262)) and under authority delegated to the Commissioner (21 CFR 5.1), § 601.25 is amended by revising paragraph (f)(4) to read as follows:

* * * * *

§ 601.25

* * * * *

[FR Doc. 78-27238 Filed 9-28-78; 8:45 am]

IV. Good Manufacturing Practices

	Page
B. Good Manufacturing Practice for Blood and Blood Components	96
3.— Blood and Blood Components	96
† 3.4 Withdrawal of Proposal—December 19, 1978 (43 FR 59098)	572
†5.—Calibration of Hematocrit Centrifuges and Vacuum Blood Agitators	573
† 5.1 Proposal—June 15, 1979 (44 FR 34515)	573
† 5.2 Final Regulation—February 12, 1980 (45 FR 9261)	574

B. Good Manufacturing Practice for Blood and Blood Components

3.—Blood and Blood Components

† 3.4 Withdrawal of Proposal—December 19, 1978

– 43 FR 59098 –

[21 CFR Part 606]

[Docket No. 76N-0109]

CURRENT GOOD MANUFACTURING PRACTICES FOR BLOOD AND BLOOD COMPONENTS; RECORDKEEPING REQUIREMENTS AND SUBMISSION

Withdrawal of Proposed Rulemaking

AGENCY: Food and Drug Administration.

ACTION: Withdrawal of Proposed Rule.

SUMMARY: The Food and Drug Administration (FDA) is withdrawing its proposal of April 30, 1976 that would have required blood and blood component facilities to record, tabulate, and submit certain data to FDA. After publication of the proposal, the American Blood Commission established the National Blood Data Center (NBDC) to collect and disseminate information relating to the blood service complex. The proposal is being withdrawn consistent with the Executive Order on Improving Government Regulations because the FDA's and the NBDC's reporting systems will generate the needed data without unnecessary duplication of effort.

FOR FURTHER INFORMATION CONTACT:

Donna C. Williams, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20014, 301-443-1306.

SUPPLEMENTARY INFORMATION: In the FEDERAL REGISTER of April 30, 1976 (41 FR 18095), the Commissioner of Food and Drugs issued a proposal to amend Title 21 Part 606 (21 CFR Part 606), good manufacturing practice regulations for blood and blood components, to require that blood and blood component facilities record, tabulate, and submit certain data to FDA. The data submitted were to be used for a product and resource survey of all blood facilities to determine the need for initiating new programs or to amend the biologics regulations to promote the continued availability of blood and blood components that are safe, pure, potent, and effective.

Over 150 comments were received by interested individuals, business firms, and professional organizations. Most comments objected to the proposed amendments and suggested that data similar to those sought by FDA were already being submitted to a variety of private, professional societies and to other Federal and State governmental agencies. The comments suggested that the FDA effort either be aborted or coordinated with that of the American Blood Commission.

After publication of the proposal, the American Blood Commission created the NBDC, whose members have been working cooperatively with members of the Bureau of Biologics, FDA, to avoid duplication of efforts in obtaining blood resource data.

The Commissioner has reconsidered the merits of a voluntary, nongovernmental blood data collection system. Voluntary programs have been conducted in the past by the Joint Blood Council (1960), the American Medical Association (1964, 1967, and 1972), and the National Heart and Lung Institute, now the National Heart, Lung, and Blood Institute (NHLBI). In a study involving over 5,000 facilities conducted by NHLBI in 1971, responses were obtained from 81 percent of the facilities surveyed, which had collected 96.5 percent of the estimated total of 9 million units of blood.

The Commissioner believes that an equal or better response is possible today under the sponsorship of the NBDC, whose sole responsibility relates to the collection and dissemination of information regarding operation of blood establishments, and that NBDC will provide the data base needed by FDA. Such a program will benefit both the agency and the public by providing for the central collection, analysis, and dissemination of statistical information useful in planning and evaluating the regulatory needs of government and furthering the goals of the National Blood Policy.

For these reasons, the Commissioner believes that the April 30, 1976 proposal should be withdrawn. This action is consistent with Executive Order No. 12044 on Improving Government Regulations in that it eliminates potential paperwork costs and other burdens to the public by eliminating unnecessary and costly duplication of efforts to obtain the blood resource data required for both FDA's and NBDC's reporting systems.

Accordingly, the Commissioner is withdrawing the proposal of April 30, 1976. The Commissioner advises all affected persons that existing data collection and retention requirements contained in the Code of Federal Regulations and/or in license applications remain in effect. In addition, this action does not affect FDA inspection authority under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act.

This withdrawal is issued under the Federal Food, Drug, and Cosmetic Act (secs. 501, 510, 701, 704, 52 Stat. 1049-1050 as amended, 1055-1056 as amended, 67 Stat. 477 as amended, 76 Stat. 794 as amended (21 U.S.C. 351, 360, 371, 374)) and under authority delegated to the Commissioner (21 CFR 5.1).

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Part 606

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[FR Doc. 78-35045 Filed 12-18-78; 8:45 am]

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†5.—Calibration of Hematocrit Centrifuges and Vacuum Blood Agitators

†5.1 Proposal—June 15, 1979

– 44 FR 34515 –

[21 CFR Part 606]

[Docket No. 78N-0439]

Calibration of Hematocrit Centrifuges and Vacuum Blood Agitators; Proposal on Calibration

AGENCY: Food and Drug Administration.

ACTION: Proposed Rule.

SUMMARY: The FDA is proposing to amend the biologics regulations to require less frequent performance checks and calibrations of hematocrit centrifuges and vacuum blood agitators. This action is being taken because the equipment is rarely subject to significant malfunctions, and because if a malfunction does occur that could affect compliance with the requirements for donor protection and the product, it is usually audibly and/or visually obvious.

DATE: Comments by August 14, 1979.

ADDRESS: Written comments to the office of the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Robert J. Meyer, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20205, 301-443-1306.

SUPPLEMENTARY INFORMATION: Section 606.60(b) of the biologics regulations (21 CFR 606.60(b)) requires the observation, standardization, and calibration of equipment used in the collection, processing, compatibility testing, storage, and distribution of blood and blood components by specifying the frequency of performance checks and calibration. The use of accurate and reliable equipment is essential for compliance with the requirements for determining donor suitability and for the manufacture of products that are safe, pure, potent, and effective. To ensure that the hematocrit centrifuge and the vacuum blood agitator are operating correctly, § 606.60(b) requires that for each day of use a performance check be conducted by standardizing the equipment with a control cell preparation and a container of known mass or volume, respectively. However, both items of equipment are not sub-

ject to significant malfunctions during their operation, and any aberrations in their expected performance that could affect compliance with the requirements for donor protection and the product are usually audibly and/or visibly obvious. Therefore, the agency concludes that the required performance checks are excessive and subject blood facilities to an unnecessary quality control burden.

Accordingly, the FDA is proposing to amend § 606.60(b) to change the presently required performance checks and frequency of calibrations and to require instead that (1) the hematocrit centrifuge be standardized and calibrated with a control preparation

- 34516 -

before initial use, after repairs or adjustments and annually and that the timer be calibrated every 3 months, and (2) the performance of the vacuum blood agitator be checked by observing the weight of the first container of blood filled for correct results each day of use and be standardized with a container of known mass or volume before initial use and after repairs or adustments.

The agency concludes that the proposed performance checks and the frequency of calibration for the hematocrit centrifuge and the vacuum blood agitator would be adequate to determine that the equipment is performing in the manner for which it was designed to ensure compliance with the requirements concerning donor suitability and the manufacture of products that are safe, pure, potent, and effective.

The agency has carefully considered the environmental effects of the proposed regulation and, because the proposed action will not significantly affect the quality of the human environment, has concluded that an environmental impact statement is not required. A copy of the environmental impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Therefore, under the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1), it is proposed that Part 606 be amended in § 606.60 by revising the entries for the hematocrit centrifuge and the vacuum blood agitator in the table in paragraph (b) to read as follows:

* * * * *

§ 606.60

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[FR Doc. 79-18518 Filed 6-14-79 8:45 am]

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†5.2 **Final Regulation—February 12, 1980**

- 45 FR 9261 -

PART 606—CURRENT GOOD MANUFACTURING PRACTICES FOR BLOOD AND BLOOD COMPONENTS

[Docket No. 78N-0439]

Calibration of Hematocrit Centrifuges and Vacuum Blood Agitators

AGENCY: Food and Drug Administration.

ACTION: Final Rule.

SUMMARY: The agency is amending the biologics regulations to require less frequent performance checks and calibrations for the hematocrit centrifuge and vacuum blood agitator. This action is being taken because the equipment is rarely subject to significant malfunctions, and because if a malfunction does occur that would affect compliance with the requirements for donor protection and the product, it is usually audibly and/or visually obvious.

EFFECTIVE DATE: March 13, 1980.

FOR FURTHER INFORMATION CONTACT: Robert J. Meyer, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20205, 301-443-1306.

SUPPLEMENTARY INFORMATION: A notice of proposed rulemaking was published in the FEDERAL REGISTER of June 15, 1979 (44 FR 34515), in which the Food and Drug Administration (FDA) proposed to amend § 606.60(b) (21 CFR 606.60(b)) to require less frequent performance checks and calibrations for the hematocrit centrifuge and the vacuum blood agitator. The proposal would require that (1) the hematocrit centrifuge be standardized

and calibrated with a control preparation before initial use, after repairs or adjustments, and annually and that the timer be calibrated every 3 months; and (2) the performance of the vacuum blood agitator be checked for correct results each day of use by observing the weight of the first container of blood filled and be standardized with a container of known mass or volume before initial use and after repairs or adjustments.

Interested persons were given until August 14, 1979, to submit written comments. Fifteen letters were received. Twelve letters expressed approval of the amendments as proposed. Other comments included in the letters and the agency's responses are as follows:

(1) Two comments asked if the proposed changes in § 606.60(b) also apply to the hemoglobinometer and blood container scale.

The agency advises that the proposed changes in § 606.60(b) specifically relate to the performance checks and frequency calibrations for the hematocrit centrifuge and the vacuum blood agitator. When satisfactory data are submitted to support a change in the required performance checks and frequency of calibrations for the hemoglobinometer and blood container scale, the agency will consider proposing changes to their performance requirements.

(2) One comment suggested that the source of the control preparation used to standardize and calibrate the hematocrit centrifuge be specified to preclude variability.

Anticoagulated blood is used for either commercial or establishment control preparations for the standardization and calibration of hematocrit centrifuges. Because the characteristics of anticoagulated blood from either commercial or establishment control preparations do not differ significantly in the determination of packed cell volume, the agency concludes that it is not necessary to specify the source of the control preparation. Accordingly, this comment is rejected.

(3) Two comments were received concerning the exclusive use of a "control cell preparation" for the standardization and calibration of the hematocrit centrifuge. One comment suggested other quality control procedures that could be effectively utilized to ensure performance instead of the control preparation.

The agency believes that the use of a control preparation for the standardization and calibration of the hematocrit centrifuge is one of the most accurate procedures to verify that the equipment will accomplish its purpose satisfactorily. The agency also recognizes that other scientifically sound procedures for calibrating the characteristics of the hematocrit centrifuge are equivalent to the control preparation method. Accordingly, § 606.60(b) has been amended in the final regulation by deleting the requirement that the hematocrit centrifuge be standardized and calibrated exclusively with a control preparation. This will permit the standardization and calibration of the hematocrit centrifuge by alternate methods that will determine if the equipment is performing in the manner for which it was designed to ensure compliance with the requirements concerning donor suitability and the manufacture of products that are safe, pure, potent, and effective.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 501, 502, 701, 52 Stat. 1040–1042 as amended, 52 Stat. 1049–1051 as amended, 52 Stat. 1055–1056 as amended (21 U.S.C. 321, 351, 352, 371)) and under the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1), Part 606 is amended in § 606.60 by revising the entries for the hematocrit centrifuge and the vacuum blood agitator in the table of paragraph (b) to read as follows:

* * * * *

§ 606.60

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[FR Doc. 80-4484 Filed 2-11-80; 8:45 am]

VIII. Bacterial Products

	Page
A. General	122
5.— Efficacy Review	122
†5.3 Final Regulation—January 5, 1979 (44 FR 1544)	576

Page

D. Specific Additional Standards for Bacterial Products 234
30.—Typhoid Vaccine 243
† 30.3 Proposal—July 17, 1979 (44 FR 41484) 585

A. General

5.—Efficacy Review

† 5.3 Final Regulation—January 5, 1979

– 44 FR 1544 –

[Docket No. 77N-0091]

PART 601—LICENSING

PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency"

AGENCY: Food and Drug Administration.

ACTION: Final Rule.

SUMMARY: The Food and Drug Administration (FDA) issues a final rule concerning the recommendations of the Panel on Review of Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency." This rule contains labeling and informed-consent requirements as well as provisions for the presence of group A streptococcus in these products.

DATES: Effective January 5, 1979; requirements for labeling are effective July 5, 1979.

ADDRESS: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Joe Holloway, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20014, 301-443-1306.

SUPPLEMENTARY INFORMATION: In the FEDERAL REGISTER of November 8, 1977 (42 FR 58266), the Commissioner of Food and Drugs published a proposal containing findings of the Panel on Review of Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency." The Panel evaluated the safety and effectiveness of 32 bacterial vaccine and bacterial antigen products and recommended that: (a) no products be placed in Category I (those biological products determined to be safe, effective, and not misbranded); (b) three products be placed in Category II (those biological products determined to be unsafe, ineffective or misbranded); (c) seven products be placed in Category IIIA (those biological products for which available data are insufficient to classify their safety and effectiveness but which may remain in the interstate commerce pending completion of testing and conformance with the recommendations of the Panel); and (d) twenty-two products be placed in Category IIIB (those biological products for which available data are insufficient to classify their safety and effectiveness and which should not continue in interstate commerce).

The Commissioner agreed with the Panel's recommendations concerning the classification of these products. Accordingly, the Commissioner announced his intention to publish a notice of opportunity for hearing to revoke the licenses for those products placed in Categories II and IIIB. The Notice of Opportunity for Hearing was published in the FEDERAL REGISTER of December 9, 1977 (42 FR 62162). Interested persons were advised that they could submit additional data in response to the revocation notices; for products placed in Category IIIA, comments or additional data concerning the classification were also invited.

In addition, the November 1977 proposal contained the Commissioner's responses to other panel recommendations concerning the testing, content, and labeling of bacterial vaccines and antigens. In view of these recommendations, the Commissioner proposed two amendments to the biologics regulations: (1) in § 601.25(h) (21 CFR 601.25(h)), to require that the labeling for Category IIIA bacterial vaccines and antigens contain a prominent boxed statement referencing the Panel's findings of insufficient data on safety and effectiveness, that written informed consent be obtained from participants in the additional studies performed pursuant to § 601.25(h), and that a patient information insert be

included with Category IIIA products continued in interstate commerce; and (2) in § 610.19 (21 CFR 610.19), to eliminate group A streptococcal microorganisms and their derivatives from bacterial vaccines and antigens. Comments on these proposals were also solicited by the Commissioner in the November 1977 proposal.

Because manufacturers of those licensed products placed in Categories II and IIIB either did not request a hearing, requested a hearing but submitted no additional data, submitted additional data which resulted in reclassification of products, or requested that the licenses be revoked, the Commissioner published in the FEDERAL REGISTER of October 27, 1978 (43 FR 50247), a notice that these licenses have been revoked. Nevertheless, the Commissioner has considered the comments submitted by patients and physicians concerning the classification of these products, as well as the comments on the proposed amendments to the biologics regulations. Interested persons were given until January 9, 1978 to file comments with the Hearing Clerk. Three hundred and twelve letters were received, many of which contained more than one comment. A summary of the comments and the Commissioner's responses are as follows:

1. Many comments supported two products which were classified in Category IIIB. These products are V-677 Streptococcus Vaccine and Entoral, both manufactured by Eli Lilly and Co. Two hundred and ninety-five comments requested reclassification of V-677 and public hearings to provide a forum for expression of the commentor's views. One hundred and five letters consisted of or included a form containing information in support of the safety and effectiveness of V-677. All of the comments contained testimonials in support of the product. The comments expressed the belief that V-677 is more effective for the treatment of arthritis than other drugs on the market and that, if V-677 is removed from the market, patients will be forced to accept the painful effects of arthritis or take drugs with dangerous side effects. In addition, the comments alleged that physicians may be subject to malpractice suits for not treating patients with the most effective drug, which, in the commentors' view is V-677. Many of the comments suggested that the costs for studies required to establish the safety and effectiveness of V-677 should be borne by the Federal government. An additional 300 comments were submitted by patients in support of the safety and effectiveness of Entoral, a cold preparation. These comments also contained reports of Entoral's value in individual cases.

The biologics safety and efficacy review procedures were first proposed in the FEDERAL REGISTER of August 18, 1972 (37 FR 16679). As stated in that proposal, because all biological products are also drugs within the meaning of the Federal Food, Drug, and Cosmetic Act, the requirements for demonstrating the effectiveness of drugs and prohibitions against their being misbranded apply to products which are also subject to the licensing provisions of section 351 of the Public Health Service Act. Although biological products have been reviewed for safety in the past, new criteria for safety, like the contemporary standards for demonstrating effectiveness, have developed in recent years.

After reviewing the comments on the proposal, the Commissioner issued a final order establishing the procedures for review of the safety, effectiveness, and labeling of biological products in the FEDERAL REGISTER of

February 13, 1973 (38 FR 4319). The preamble to that final order discussed the requirements that biological drugs be shown to be both safe and effective for all their intended uses.

Section 601.25 governing the review of biological products contains standards for safety and effectiveness. Section 601.25 provides that "proof of effectiveness shall consist of controlled clinical investigations," unless this requirement is waived on the basis of a showing that it is not reasonably applicable to the biological product or essential to the validity of the investigation. Alternate methods of investigation are appropriate only if they are "adequate to substantiate effective-

ness." Although the regulations provide that partially controlled or uncontrolled studies, as well as significant human experience, may be used to corroborate controlled clinical studies, isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered in support of the effectiveness of the drug. (See § 601.25(d)(2).) Section 601.25(d)(3) authorizes the panels to consider the benefit-to-risk ratio in determining safety and effectiveness.

Since promulgation of the regulations governing the review of the safety, effectiveness, and labeling of all biological products, the Supreme Court has reaffirmed that controlled clinical investigations constitute the contemporary standard and represent the well-established principles of scientific investigation. (See *Weinberger v. Hynson, Westcott and Dunning, Inc.*, 412 U.S. 609 (1973).) Based upon the regulations and the law, the Commissioner finds that the testimonials submitted in support of V-677 and Entoral are not an acceptable alternative to scientifically valid proof of the safety or effectiveness of these products. As the Supreme Court noted, anecdotal reports about drug safety and effectiveness are, unfortunately, "treacherous." "The Panel concluded that the effectiveness and safety of treatment with a product for a given disease can be judged properly by adequate and well-controlled studies on populations of patients having the most well-defined disease states and carefully selected to be as homogenous as possible." (See the November 1977 proposal at 42 FR 58270 under "Areas of Panel Concern.") The Panel did, however, attempt to identify information that would corroborate the testimonial evidence and unconfirmed and uncontrolled clinical impressions that it received from both producers and individuals. Alternative methods for adequate and well-controlled studies were considered. None of these alternatives was considered to be sufficient to establish definitive effectiveness, for reasons articulated in the evaluation of each product. About safety, the Panel noted that safety claims "were based primarily upon the manufacturer's reports of adverse reactions. This might have been satisfactory had there been some evidence of systematic followup by physicians for the late, and perhaps subtle, adverse effects that might be associated with repeated inoculations. In view of what is known from laboratory studies about the potential risks associated with repeated inoculations of foreign substances, the Panel was left with reservations about the long-term safety of the subject products." (See the November 1977 proposal at 42 FR 58270-58271 under "Safety.") The Panel concluded that it "could not recommend waiver of these requirements [21 CFR 601.25(d)] on the basis of claims that a controlled clinical trial is not feasible because of lack of funding, lack of interest, or difficulty in obtaining a sufficient number of patients." (See the November 1977 proposal at 42 FR 58271 under "Panel Specific Product Reports and Reviews.")

The Panel's report reflects the careful consideration that the Panel gave to physician and patient reports submitted in support of licensed products. The Panel issued a position statement which was "prompted in large part by the expressed fears of many practicing physicians that Panel members will make arbitrary decisions and that the findings of doctors who had used these biologicals for many years will be discounted without careful consideration. This is not the intent of the Panel * * *." (See the November 1977 proposal at 42 FR 58272 under "Extent to Which Prior Use of These Products Can Be Used To Satisfy Present Standards of Safety and Effectiveness.") This statement makes clear that the views of those persons who have submitted comments on the Commissioner's proposal have already been thoughtfully considered. In discussing its evaluation of safety, the Panel identified exactly those problems which establish the need for scientifically valid and controlled studies: the lack of an effective mandatory system for reporting adverse reactions, that a practicing physician sees only a limited number of patients and therefore will identify only adverse reactions that occur at a very high rate, that patients with severe reactions

may not return to the same treatment situation, and that a causal relationship is difficult to discern due to the time and other events between the administration of a drug and the onset of the adverse reaction. The Panel's summary clearly shows that every effort was made to give all reasonable credit to significant human experience during marketing. (See the November 1977 proposal at 42 FR 58272 under "Summary.")

The Commissioner notes that nondeliberative portions of all meetings of the Panel were open to the public. Announcements of the meetings were published in the FEDERAL REGISTER before each meeting, and interested persons were given an opportunity to make presentations to the Panel. No person who requested an opportunity to appear and make a presentation was denied that request. In addition, as part of the process of nominating qualified experts to serve on the Panel, the Commissioner issued letters to approximately 35 medical and scientific associations and consumer groups advising them of the review of bacterial vaccines and bacterial antigen products. Ample opportunity was given for public participation in the proceedings, and manufacturers had adequate time and opportunity to present additional data in support of continued licensure for their products. For these reasons, the request that additional public hearings be provided to present a forum for those disagreeing with the Panel's recommendations and the Commissioner's conclusions is denied.

The Panel reviewed and evaluated the reports submitted in support of the safety and effectiveness of V-677. As to effectiveness, the Panel found that the only "controlled" study was inadequate, that its result was inconclusive and that it "does not provide the data required for a positive judgment of the safety or effectiveness of V-677." (See the November 1977 proposal at 42 FR 58290 under b. *Effectiveness.*) The Panel concluded that the study had "deficiencies which seriously impair current usefulness." As to safety, the Panel concluded that the available data supporting the presumed safety of the product "may be more apparent than real" and that reported observations "posed questions of safety with regard to the chronic injection of such material into humans." (See 42 FR 58290 under a. *Safety.*) The Panel placed V-677 in Category IIIB because there is no substantial evidence of safety or effectiveness nor is there even evidence presumptive of safety.

The Panel reviewed the data submitted in support of Entoral's effectiveness and concluded that although the labeling for the product was cautiously worded, "the statement on use of the vaccine does imply effectiveness, but the implication is not supported by the evidence." (See the November 1977 proposal at 42 FR 58286 under c. *Labeling.*) The Panel found that "the vaccine has long since been put to the test of controlled clinical studies and found wanting." (See 42 FR 58286 under a. *Critique.*) None of the studies

reviewed by the Panel demonstrated claims for effectiveness. The Panel concluded that there was neither substantial nor presumptive evidence of effectiveness of Entoral.

The Commissioner adopted the Panel's recommendations on V-677 and Entoral and proposed that they be placed in Category IIIB. A notice of opportunity for hearing on the revocation of the license of Entoral was not published since the license for Entoral was revoked at the request of Eli Lilly and Co. on April 11, 1977.

In response to the notice of opportunity for hearing concerning V-677, Eli Lilly and Co. did not request a hearing or submit any data. Accordingly, their license was revoked. (See the October 27, 1978 Notice.)

The Commissioner advises that an opportunity for a hearing is directed to the manufacturer of a product whose license is the subject of the proposed revocation. If a hearing is requested by a manufacturer and granted, all interested parties may present evidence regarding the proposed revocation (21 CFR 12.45). However, in view of the failure by Eli Lilly and Co. to request a hearing, no further proceeding is available.

The Commissioner notes that there are numerous drugs other than V-677 which are marketed for the treatment of arthritis. For this reason, the Commissioner rejects the suggestion that revocation of the V-677 license will cause substantial adverse effects for current users of V-677 who must now select other arthritis drugs. Drugs recommended for treatment of arthritic conditions, like every other drug, have the potential for causing some side effects in some individuals. Generally, it is the responsibility of the physician prescribing these drugs to weigh the benefits against the risks involved in treatment of each individual patient and to ensure that the patient gains the maximum benefits with the least possible risks.

The Commissioner also notes that the classification of a product into Category IIIB does not preclude further studies. It requires only that the product not be marketed commercially while controlled studies are conducted in accordance with the IND provisions of the law. Those persons being treated with V-677 may serve as test subjects for the IND clinical trials. This mechanism provides for continued availability of a drug but only as part of a plan to study its safety and effectiveness. This mechanism also provides maximum protection to the test subjects. Thus, although the Eli Lilly and Co. licenses for both Entoral and V-677 have been revoked, the law does not prohibit investigational new drug use of either drug.

2. Thirteen comments, primarily from practicing physicians, asserted that Hoffmann Laboratories' Respiratory Bacterial Antigen Complex (BAC), and Pooled Skin BAC are effective for upper respiratory and skin infections and cause no known side effects. These comments requested that these products be reclassified.

The Panel recommended that the Respiratory BAC be placed in Category IIIA on the condition that it not contain group A streptococcus strains and that the labeling state in standard medical terminology the specific indications for use. (See the November 1977 proposal at 42 FR 58296.) The Panel recommended that the Pooled Skin BAC be placed in Category IIIB. For both products, the Panel concluded that there was no substantial evidence of safety and effectiveness. The Panel found some presumptive evidence of safety for the respiratory BAC products but no presumptive evidence of safety for the pooled skin products. These conclusions were based on an extensive review of the data submitted in support of these products and, as specifically noted by the Panel, upon the consideration of numerous "letters, depositions, and reports from physicians and patients supporting the efficacy of respiratory BAC product." (See the November 1977 proposal at 42 FR 58295.) The Panel noted that the support for the effectiveness of these preparations in humans in "based entirely on uncontrolled studies, case reports, letters, and depositions from physicians and their patients." (See 42 FR 58295 under (2) *Effectiveness.*) The Panel found that the indications for use in the labeling "are extremely broad," and that the "present state of knowledge neither proves nor disproves the possibility that bacterial antigens or vaccines in general or these products in particular induce either of the [claimed] effects." The Panel also felt that the package insert "is totally inadequate" in guiding the physician user's selection among the four products marketed. "Published articles supplied by the manufacturer, at the specific request of the physician, failed to provide adequate guidance." (See the November 1977 proposal at 42 FR 58296 under (4) *Labeling.*) Hoffmann Laboratories requested the revocation of their licenses for the manufacture of all of their licensed biological products. The comments recommending that these products be upgraded are rejected.

3. The Panel recommended that the Federal government sponsor some of the studies required to establish the safety and effectiveness of bacterial vaccines and bacterial antigen products. In response to that recommendation, the Commissioner noted that the regulations provided for such studies in § 601.25(h)(1) and acknowledged that such studies may be desirable and beneficial. Accordingly, the Commissioner solicited comments on the pro-

posal by the Panel for the expenditure of Federal funds to study these products.

In response to that invitation, seven comments were received, all of which supported the expenditure of Federal funds for additional studies of products in Category IIIA. The comments suggested that Federal support was necessary because the cost for the required studies would be prohibitive for small manufacturers. In view of the Panel's recommendation and the responses submitted, the Director, Bureau of Biologics, will notify the appropriate Federal agencies so that such studies may be considered and priorities assigned. The FDA budget does not provide for developmental research in support of marketed products because the law places this burden upon the proponent or manufacturer.

4. Two comments suggested that the Commissioner permit ineffective bacterial vaccines to remain on the market as placebos for psychological effects.

Ineffective drugs may not be lawfully sold or distributed in interstate commerce. Such drugs are misbranded and are new drugs within the meaning of the Federal Food, Drug, and Cosmetic Act. Unlike true placebos, ineffective drugs may cause physiological or pharmacological effects in addition to the psychological (placebo) effects. Therefore, the use of ineffective drugs as placebos is inconsistent with sound medical practice. Accordingly, the comments are rejected.

5. Two comments objected to the statement in item 1b. of the proposal's preamble at 42 FR 58315, that "safety and effectiveness of the products rest largely upon information, in the form of anecdotes and results of informal studies, which were collected during the long years of use of the products." The comments state that the statement is not true for some products placed in Category IIIA by the Panel. However, the comments did not identify any specific product or provide data to support their objection.

The Commissioner advises that the Panel's conclusions were based on data the manufacturers submitted in support of the products, other medical literature, and oral presentations by interested persons and manufacturers at the Panel's meetings. The statement in item 1b. of the proposal's preamble applies to all products placed in Category IIIA. Therefore, the comments are rejected.

6. One comment noted that *Staphylococcus albus* and *Staphylococcus*

aureus were incorrectly listed as components of the Hollister-Stier products classified as Category IIIB by the Panel. The organisms should have been listed as components of the Hollister-Stier products that were classified as Category IIIA by the Panel.

The Commissioner agrees with this comment. Therefore, the organism listing of *Staphylococcus albus* and *aureus* is corrected on the official agency copy of the proposal. This correction was also made in a notice published in the FEDERAL REGISTER of October 27, 1978.

7. One comment suggested that the Commissioner require in vivo studies in humans before a drug is marketed because treatment is usually given to a patient with a complicated disease process and in vitro results do not necessarily forecast the actual effects of the drug when used in humans.

The Commissioner advises that the requirements in §§ 601.21 and 601.25 already preclude the marketing of a drug in interstate commerce until there is substantial evidence of effectiveness derived from adequate and well-controlled investigations, including clinical investigations. Such studies include use in susceptible persons and should be sufficient to establish the pharmacological effects of the drug when used in the manner and by the mode of administration suggested in the manufacturer's labeling. Accordingly, the Commissioner believes there is no apparent need to change this requirement and the comment is rejected.

8. In conjunction with the proposal to place certain products in Category IIIA and in view of the Panel's conclusions concerning the effectiveness of Category IIIA drugs, the Commissioner proposed that (1) the circular and promotional material for these drugs

must have a prominent boxed statement referencing the need for further data to fully establish effectiveness; (2) written informed consent be obtained from participants in the requisite additional studies, an explanation of the product and the purpose of the study be given to such participants, and a clear opportunity be provided to them to refuse to participate in the study; and (3) a printed patient insert be included with all Category IIIA Bacterial Vaccines and Bacterial Antigens which have been designated as having "No U.S. Standard of Potency" continued in interstate commerce. The requirements for the boxed warning and informed consent were the same as those proposed by the Commissioner in the FEDERAL REGISTER of September 30, 1977, in the proposal concerning the implementation of the report of the Panel on Review of Skin Test Antigens.

One comment was received in response to the proposed labeling. It stated that the requirement for a prominent boxed warning will cause a marked reduction in the use of the products identified with this notice.

As the Commissioner noted in the proposal, the conclusion by an expert panel that the data in support of the products' safety and effectiveness are currently insufficient is a material fact within the meaning of section 201(n) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(n)) and the failure to disclose this fact is misleading, resulting in the products being misbranded. Moreover, the Commissioner believes that it is essential that patients and physicians be aware of the lack of controlled studies in support of a product. In addition, the Commissioner notes that a boxed warning concerning the results of expert panel reviews has been used for many years in conjunction with drugs which were the subject of the efficacy review panels in the 1960's. (See § 201.200 (21 CFR 201.200).) Accordingly, the comment is rejected.

However, the Commissioner has decided that the adoption of the boxed warning and written informed consent for participants in studies conducted on Category IIIA products (§ 601.25(h)(4) and (5)) should be promulgated upon specific notice to those persons affected by the review of each category of biological products. Accordingly, this final order imposes these requirements for Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency" only. When the final order is published for skin test antigens, the Commissioner will consider the application of these requirements to those particular products.

9. Three comments from manufacturers and manufacturer associations stated that § 610.25(h)(6) should not be amended to require a printed patient insert because the presence of a printed patient insert may result in the patient's refusal to take medications bearing such labeling. One comment stated that FDA has no legal authority to require such patient labeling.

FDA is charged with assuring that licensed biologics are safe and effective for their intended uses and that essential information concerning contraindications and warnings is fully disclosed to physicians. Accordingly, the Commissioner has reviewed the recommendations of the Panel regarding Category IIIA products, taking into account the following factors. The Panel stated:

> Justification for placing products in Category IIIA is presumptive evidence of effectiveness and safety. Although not clearly stated, the implication is that such suggestive evidence can be largely derived from the fact that many of the products have been widely used for many years and that although systematic rigorous trials may not have been done, the lack of reported dangerous side effects over a period of many years indicates in itself at least a certain degree of safety. Effectiveness can be looked at in the same way.

The Panel also noted that:

> Claims for safety were based primarily upon the manufacturers' reliance on long marketing experience and infrequent physicians' reports of adverse reactions. This might have been satisfactory had there been some evidence of systematic followup by physicians for the late, and perhaps subtle, adverse effects that might be associated with repeated inoculations. In view of what is known from laboratory studies about the potential risks associated with repeated inoculations of foreign substances, the Panel was left with reservations about the long-term safety of the subject products.

These products are administered repeatedly and over long periods of time. The medical profession generally recognizes that other therapies are available for the conditions for which these products are used. There is no present assurance that persons treated with these products are being made aware of the potential for risk or of the availability of alternative modes of treatment.

It was for these reasons that the Panel explicitly stated:

Vaccines and antigens that have been recommended for Category IIIA, i.e., licensure permitted to continue for a limited time while further studies are done, require separate considerations on labeling.

* * * Useful information about safety and effectiveness should be provided directly to patients who receive products continued in use. The package insert or circular used to satisfy the need for consumer information should contain the updated information provided to the prescribing physician. The package insert or circular given to the patient and physician should also state in boldface, at the beginning, that this product is under review by FDA for a limited time since safety and effectiveness have not been substantially established. In particular, it should be noted that adequately controlled human trials have not been done.

Accordingly, the Panel recommended that the labeling "include a patient information insert."

In view of the foregoing, the Commissioner concludes that it is in the public interest to provide users of these particular Category IIIA products with notice of those factors that concerned the Panel.

Therefore, the Commissioner also concludes that a procedure must be developed for providing this information to prospective users of these products. A proposed procedure is now being developed by the agency and will be published in the FEDERAL REGISTER as soon as possible.

- 1548 -

The Commissioner notes, and concurs with the Panel's finding regarding, the specific characteristics of these products which distinguish them from other licensed biologics and from other drugs, and which therefore make it necessary, in the judgment of the Panel and the Commissioner, to provide information to prospective users. In this respect the Panel stated:

While all licensed biologics are undergoing reviews for safety, effectiveness, and appropriateness of labeling at this time, the products assigned to this Panel have several characteristics that distinguish them from other categories of vaccines and antigens.

This finding resulted from problems summarized by the Panel as follows:

1. The etiologies and pathogeneses of many conditions treated with "bacterial vaccines and antigens" and the way in which they might prevent or alleviate the pathologic state are not well understood.

2. The causal relationships of the species or strains of vaccine organisms (or derivatives) to the diseases for which they are prescribed are generally unclear.

3. Standards of potency are needed, including precise identification of the contents of the finished products.

4. Patients treated for many of the recommended conditions represent highly heterogeneous subgroups whose conditions and symptoms are noticeably labile and difficult to characterize objectively. These subpopulations should be defined and identified.

5. Data on the rate and significance of spontaneous remissions in the chronic disorders for which these products are used are not available.

6. The rationale by which the selection of bacterial strains for incorporation in a given product often was either not clear or not stated.

7. The need to include different bacterial strains (and species) into one vehicle was not documented.

It should be noted that the policy to require labeling directed to the patient for certain prescription products as required by specific circumstances is already established and being followed by the agency. (See § 310.501, as amended in the FEDERAL REGISTER of January 31, 1978 (43 FR 4214) for oral contraceptives; § 310.515 (21 CFR 310.515), promulgated by final order published in the FEDERAL REGISTER of July 22, 1977 (42 FR 37636) for estrogenic drugs; and § 310.516 (21 CFR 310.516), promulgated by final order published in the FEDERAL REGISTER of October 13, 1978 (43 FR 47178) for progestational drugs.) The authority to promulgate patient package insert information for drugs, including biological drugs subject to section 351 of the Public Health Service Act, is stated in the preambles of these final orders, as well as in the general label-

ing proposal published in the FEDERAL REGISTER of April 7, 1975 (40 FR 15392). This authority has been preliminarily upheld by the one court that has reviewed the issue (*Pharmaceutical Manufacturers Association* v. *FDA*, Civ. No. 77-291 (D. Del., October 5, 1977) (order denying preliminary injunction)). For a general explanation of FDA's rulemaking authority, see *National Nutritional Foods Association* v. *Weinberger*, 512 F.2d 688, 695-698 (2d Cir. 1975).

10. Two comments on proposed § 610.19 suggested that the regulation should be redrafted because it now appears to prohibit the use of group A streptococcus organisms under all circumstances.

The Commissioner advises that § 610.19 (21 CFR 610.19) prohibits the interstate marketing of any Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency" which contain group A streptococcus organisms and their derivatives. However, the regulation does not prohibit the presence of these organisms in bacterial products subject to investigation under the investigational new drug provisions of the law and consistent with 21 CFR Part 312. The Commissioner finds the currently drafted regulation clear and rejects the comment.

The Commissioner considered the comments and other relevant information and concludes that the proposal on the Panel's recommendations concerning the classification of products into Categories I, II, IIIA, and IIIB should be and is hereby adopted, with changes, as set forth below.

a. Category I—*Biological products determined to be safe and effective and not misbranded that should continue in interstate commerce.* None of the Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency" was placed into this category.

b. Category II—*Biological products determined to be unsafe or ineffective or to be misbranded that should not continue in interstate commerce.* Product licenses for Category II products were revoked as announced in the FEDERAL REGISTER notice of revocation and reclassification on October 27, 1978 (43 FR 50247).

c. Category IIIA—*Biological products for which available data are insufficient to classify their safety and effectiveness but which may remain in interstate commerce.* Respiratory UBA (UBA-32) manufactured by Eli Lilly and Co., license No. 56; Respiratory B.A.C. manufactured by Hoffmann Laboratories, Inc., license No. 283; Staphylococcal B.A.C. manufactured by Hoffmann Laboratories, Inc., license No. 283; Bacterial Vaccines Mixed Respiratory (MRV or MRVI) manufactured by Hollister-Stier, Division of Cutter Laboratories, license No. 8; Bacterial Vaccines for Treatment, Special Mixtures containing only the following organisms—*Staphylococcus* (*aureus* and *albus*), *Streptococcus* (*viridans* and nonhemolytic) *Diplococcus pneumoniae, Neisseria catarrhalis, Klebsiella pneumoniae, Haemophilus influenzae* manufactured by Hollister-Stier, Division of Cutter Laboratories, license No. 8; Staphylococcus Toxoid Sclavo manufactured by Istituto Sieroterapico Vaccinogeno Toscano "Sclavo," license No. 238; Staphylococcus Toxoid; Formalinized: Dilution No. 1, Dilution No. 2; Digest-Modified manufactured by Lederle Laboratories Division, license No. 17; and Staphage Lysate (SPL) Type I and Types I and III combined manufactured by Delmont Labs, Inc., license No. 299. Licenses remain in effect for these products pending conformance with the Panel's recommendations and completion of testing (except that, at the request of Hoffmann Laboratories, Inc., their license to manufacture Respiratory B.A.C. and Staphylococcal B.A.C. was revoked as announced in the October 27, 1978 FEDERAL REGISTER notice of revocation and reclassification).

For products now herein classified in Category IIIA for which license revocations have not been issued at the request of the licensee, manufacturers shall submit, within 30 days following publication of this order, a written statement of those studies which the licensee proposes to undertake to resolve the questions raised about the products. If no such commitment is made or adequate or appropriate studies are not undertaken, the Commissioner shall institute proceedings to revoke the license (21 CFR 601.25(h)(1)). Licenses for Category

products will remain in effect ding the conduct of studies as rec- nended by the Panel and adopted the Commissioner. Labeling nges recommended by the Panel now adopted by the Commissioner ll become effective on July 5, 1979. ause data submitted by Delmont oratories, Inc., have been found to adequate to reclassify its staphage te types I and II combined, license 299, from Category IIIB to IIIA, requirements concerning comple- n of testing and labeling apply to se products.

dditional background data and in- mation on which the Commissioner es in promulgating these regula- ns are on public display in the ce of the Hearing Clerk (HFA-305), od and Drug Administration, Rm. 4- 5600 Fishers Lane, Rockville, MD 57.

herefore, under the Federal Food, g, and Cosmetic Act (secs. 201, 502, , 701, 52 Stat. 1040-1042 as amend- 1050-1053 as amended, 1055-1056 amended by 70 Stat. 919 and 72 t. 948 (21 U.S.C. 321, 352, 355,)), the Public Health Service Act c. 351, 58 Stat. 702 as amended (42 .C. 262)), and the Administrative

ocedure Act (secs. 4, 10, 60 Stat. 238 d 243 as amended (5 U.S.C. 553, 702, , 704)), and under authority dele- ed to the Commissioner (21 CFR), Parts 601 and 610 are amended as llows:

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§ 601.25

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§ 610.19

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[FR Doc. 79-227 Filed 1-4-79; 8:45 am]

. Specific Additional Standards for Bacterial Products

—Typhoid Vaccine

).3 Proposal—July 17, 1979

- 44 FR 41484 -

[21 CFR Part 620]

[Docket No. 78N-0425]

Bacterial Products; Additional Standards for Typhoid Vaccine

AGENCY: Food and Drug Administration.

ACTION: Proposed Rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the biologics Typhoid Vaccine regulations to ensure further the antigenic integrity of the Ty 2 strain of bacteria used in vaccine production and to require that licensed manufacturers obtain the U.S. Opacity Standard from the Bureau of Biologics. The FDA is also proposing to amend these regulations by establishing new standards for the performance and results of the potency test for each lot of manufactured Typhoid Vaccine.

DATES: Comments by September 17, 1979.

ADDRESS: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Michael L. Hooton, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20014, 301-443-1306.

SUPPLEMENTARY INFORMATION: The Commissioner is proposing to amend the biologics regulations for manufacturing Typhoid Vaccine by setting potency standards for the Ty 2 strain of *Salmonella typhosa* used in the manufacture of Typhoid Vaccine and by revising the potency test under § 620.13 (21 CFR 620.13) consistent with new scientific knowledge derived from past experience with the product.

In the United States, typhoid disease has been in decline in recent years and routine typhoid vaccination is no longer recommended. However, immunization is indicated if a person has come into contact with a known typhoid carrier, if there is an outbreak of typhoid fever in the community, or if a person plans to travel to an area where typhoid fever is endemic.

Under section 351 of the Public Health Service Act (42 U.S.C. 262), Typhoid Vaccine offered for sale, barter, or exchange in interstate commerce must be licensed and meet certain standards that ensure its continued safety, purity, potency, and effectiveness. Minimum requirements for Typhoid Vaccine were first established on December 8, 1953, and revised on September 30, 1966. Additional standards were published in the FEDERAL REGISTER on June 4, 1969 (34 FR 8914) and recodified as §§ 620.10 through 620.15 (21 CFR 620.10 through 620.15), on November 20, 1973 (38 FR 32048). Under § 620.14(c) of the additional standards (21 CFR 620.14(c)), Typhoid Vaccine shall not be issued by the manufacturer until written notification of official release is received from the Director, Bureau of Biologics (BOB). Official written release is issued only after the Director has reviewed the protocol and tested samples to ensure the continued safety, purity, potency, and effectiveness of Typhoid Vaccine.

On the basis of new scientific knowledge derived from product release data accumulated and analyzed by BOB for the past several years, FDA is proposing amendments to the additional standards for Typhoid Vaccine, including the following:

(1) Strain Ty 2 of *Salmonella typhosa* is used in the manufacture of Typhoid Vaccine. To ensure the antigenic integrity of the Ty 2 strain, FDA is proposing to amend § 620.11 (21 CFR 620.11) to require that antigenic integrity be verified by the agglutination of living bacteria by a Ty 2 antiserum.

(2) To clarify the source for obtaining necessary reference materials, FDA proposes to amend § 620.12 (21 CFR 620.12) to require that the U.S. Standard Typhoid Vaccine and the U.S. Opacity Standard be obtained from the Bureau of Biologics.

(3) Saline is required for use in dilutions of the vaccine and challenge doses used in the potency test. The use of phosphate-buffered saline (PBS) by the BOB has not resulted in any detectable changes in the potency test. Accordingly, FDA is proposing to amend § 620.13(b)(1) and (c)(2) to permit the use of PBS for diluting the vaccine, the challenge, and virulence titrations of Strain Ty 2 of *Salmonella typhosa*.

(4) Based on statistical methods used in, and results derived from, Typhoid Vaccine potency tests performed at the BOB, FDA is proposing to amend § 620.13(e) to require that new statistical methods be used for determining the validity of the potency test. For consistency, FDA proposes to amend

§ 620.13(g) to eliminate the requirement that the standard deviation be used as the basis for calculating the ED_{50} of each lot of Typhoid Vaccine.

(5) Based on test data accumulated and analyzed by the BOB, the agency has determined that existing § 620.13(e)(6) should be amended to change the maximum challenge dose of typhoid bacteria from 10 to 20 colony forming units per LD_{50}. This change, as found in § 620.13(e)(7) of the proposed amendments, would decrease the frequency of repeat tests that may be necessary to meet the criteria for test validity.

(6) Consistent with the changes proposed in § 620.13(e) and due to the statistical significance of the biological variations encountered in Typhoid Vaccine potency testing, FDA is proposing to amend § 620.13(f) to prescribe conditions for repeat potency tests and to require that the results of not more than four valid tests be used for determining that Typhoid Vaccine meets the potency requirements.

(7) The agency has determined that the potency test is of such a variable nature that it necessitates at least two separate assays of the required potency test on each lot of Typhoid Vaccine before submission to the BOB. Accordingly, FDA is proposing to amend § 620.13(h) to require that the results of at least two separate tests be submitted to the BOB, and to prescribe potency requirements based on the results of at least two, but no more than four, tests. From the statistical data accumulated and analyzed in the potency testing of Typhoid Vaccine, FDA is also proposing new minimum values based on the number of tests performed, for

the geometric mean relative potency for each lot.

Pertinent background data on which the agency relies in proposing these amendments are on public display in the office of the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FDA has carefully considered the environmental effects of the proposed regulation and, because the proposed action will not significantly affect the quality of the human environment, has concluded that an environmental impact statement is not required. A copy of the environmental impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Therefore, under the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)) and under authority delegated to the Commissioner (21 CFR 5.1), it is proposed that Part 620 be amended as follows:

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Part 620

§ 620.11
§ 620.12
§ 620.13

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[FR Doc. 79-22000 Filed 7-16-79; 8:45 am]

IX. Viral Vaccines

	Page
D. Specific Additional Standards for Viral Vaccines	259
10.—Bacillus of Calmette and Guerin (BCG) Vaccine	261
† 10.2 Final Regulation—March 13, 1979 (44 FR 14541)	587
35.—Mumps Virus Vaccine, Live	266
† 35.3 Notice—May 16, 1978 (43 FR 21052)	596

D. Specific Additional Standards for Viral Vaccines

10.—Bacillus of Calmette and Guerin (BCG) Vaccine

10.2 Final Regulation—March 13, 1979

– 44 FR 14541 –

[Docket No. 78N-0333]

PART 620—ADDITIONAL STANDARDS FOR BACTERIAL PRODUCTS

BCG Vaccine

AGENCY: Food and Drug Administration.

ACTION: Final Rule.

SUMMARY: The Food and Drug Administration (FDA) issues additional standards for the manufacture of Bacillus of Calmette and Guerin (BCG) Vaccine. BCG Vaccine is a freeze-dried preparation containing viable bacteria of the Bacillus of Calmette and Guerin, an attenuated strain of *Mycobacterium bovis*, used for the prevention of tuberculosis. The additional standards reflect advances in scientific knowledge and technology.

DATES: Effective May 11, 1979, except for labeling requirements, which are effective September 13, 1979.

FOR FURTHER INFORMATION CONTACT:

Donna Williams, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20014, 301-443-1306.

SUPPLEMENTARY INFORMATION: In the FEDERAL REGISTER of March 18, 1974 (39 FR 10158), the Commissioner of Food and Drugs proposed to amend the biologics regulations by adding new additional standards for the manufacture of BCG Vaccine. The new standards contain many provisions of the uncodified "Minimum Requirements," developed in 1945, that have been used as the primary guide for licensing the production, testing, and distribution of BCG Vaccine. The standards also contain significant changes and additions that reflect more recent advances in science and technology and that are necessary to ensure a uniform high quality of licensed BCG Vaccine. These standards apply to the manufacture of BCG Vaccine for its well-established use as an immunizing agent against tuberculosis, but not for its more recent use in experimental immunotherapy for cancer and leukemia. Those persons

wishing to investigate the effectiveness of BCG Vaccine in cancer research must submit a "Notice of Claimed Investigational Exemption for a New Drug" to the Bureau of Biologics, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20014.

The proposal incorrectly codified the new standards into Part 630—Viral Vaccines (21 CFR Part 630). The final regulations are issued in Part 620—Bacterial Vaccines (21 CFR Part 620). The Commissioner is making a significant number of editorial changes in the final regulations. The sections are rearranged to be consistent with other previously issued standards in Part 620. The following are the section numbers as originally proposed and their corresponding redesignated numbers in this final rule:

March 1974 proposal	Redesignated as
630.90 *BCG Vaccine*	620.40 *BCG Vaccine.*
630.92 *Establishment and personnel requirements.*	620.41 *Establishment and personnel requirements.*
630.92 *Reference BCG Vaccine.*	620.43 *Reference BCG Vaccine.*
630.93 *Manufacture of BCG Vaccine.*	620.42 *Production.*
630.94 *Test for freedom from virulent mycobacteria.*	620.45 *Test for freedom from virulent mycobacteria.*
630.95 *Potency tests*	620.44 *Potency tests.*
630.96 *General requirements.*	620.46 *General requirements.*
630.96(c) *Labeling*	620.47 *Labeling.*
630.97 *Samples; protocols; official release.*	620.48 *Samples; protocols; official release.*
	620.49 *Equivalent methods.*

Interested persons were given until May 17, 1974 to file written comments with the Hearing Clerk, FDA, regarding the proposal. Four letters, each containing a number of comments, were received. Throughout this preamble, the new section numbers are used. The comments and the Commissioner's responses, including discussion of changes made since the proposal was issued, are as follows:

Criteria for an Acceptable Strain

1. One comment on proposed § 620.40(b)(2) (21 CFR 620.40(b)(2)) stated that the number of guinea pigs (48) required to test the primary seed lot for freedom from virulence is excessive. The comment recommended adopting the World Health Organization (WHO) criteria paragraph 3.1.3, which provides for the use of at least 10 guinea pigs to test the seed lot and requires that 60 percent survive an observation period of at least 6 months. The comment stated, incorrectly, that paragraph 5.3.1 of the WHO criteria requires that at least 6 guinea pigs be used to test secondary seed lots and that two-thirds of the test animals must survive the period of observation of from 6 weeks (Copenhagen) to 3 months (Japan). The comment claimed that these criteria, WHO Technical Report Series, 1966, No. 329, had been used for more than 20 years and had been found completely satisfactory.

The Commissioner advises that paragraph 5.3.1 of the WHO report applies to "each vaccine lot • • •." The comment misinterpreted paragraph 5.3.1 by applying it to a "secondary seed lot." A "secondary seed lot" and a "vaccine lot" are two entirely different stages in the manufacture of BCG Vaccine. "Secondary seed lot," as used in the additional standards, is material obtained from a primary seed lot that has been increased in quantity by serial passages in growth-promoting media, dispensed in smaller aliquots, and stored in the freeze-dried or frozen state. A sample of the secondary seed lot is subsequently used as starting seed for the production of the lot of final container material. Paragraph 5.3.1 of the WHO report describes a test for the absence of virulent mycobacteria in each "vaccine lot." Paragraph 1.4 of the WHO report defines a "vaccine lot" as "Vaccine in final containers from a single final bulk subsequently processed together and which had, therefore, a uniform composition before drying." The paragraph further explains that a "final lot" is material in final containers filled in one working session and dried together, and that a final lot may consist of all or part of a vaccine lot. Thus, a "vaccine lot," as that term is used by WHO, is finished final container material, and a "secondary seed lot," as that term is used by FDA, is many manufacturing steps before finished container material. Because paragraph 5.3.1 testing does not apply to a secondary seed lot, the Commis-

sioner cannot compare that test procedure to the test required by the addi-

tional standards and must reject the comment.

The Commissioner disagrees with the comment, which referenced paragraph 3.1.3 of the WHO report, that the number of guinea pigs (48) required to test the primary seed lot is excessive. The purpose of the test is to ensure that no virulent mutants capable of causing progressive tuberculosis in animals have arisen. These data are necessary before starting clinical trials in humans. A primary seed lot material lasts for decades, and each secondary seed lot lasts for many years. The safety characteristics of these basic starter substances determine, in large degree, the safety of vaccine for use in humans. The Commissioner has concluded that greater testing of seed material is necessary. Accordingly, the recommendation to reduce the number of test animals is rejected.

2. One comment on proposed § 620.40(b)(4) stated that it would be preferable to vaccinate persons who are negative to 250 U.S. Tuberculin Units, Purified Protein Derivative (PPD) (250 TU) rather than to the proposed 5 TU test dose. The comment gave no reason why the suggested larger dose was preferable.

The Commissioner advises that 5 TU was proposed as the most suitable test dose because the subjects to be selected for vaccination should be free of infection with *M. tuberculosis*. The 250 TU test dose will detect many persons infected with other mycobacteria and will cause a boosting effect in some individuals that will convert these individuals classified as tuberculin negative to tuberculin positive. Should the BCG vaccination be administered shortly thereafter, the effects of the boosting would complicate interpretation of sensitivity induced by the vaccine. Such boosting effect is not as likely to occur in persons receiving a 5 TU test dose. Accordingly, the comment is rejected.

3. One comment on proposed § 620.40(b)(4) stated that a tuberculin conversion rate (the proportion of persons developing tuberculin reactivity after vaccination with BCG Vaccine) of at least 90 percent can be achieved only if a test dose of 250 TU is used for the postvaccination test. The comment recommended that if the test dose is 5 or 10 TU, as proposed, the conversion rate be lowered from 90 percent to 80 percent.

The Commissioner advises that manufacturers who have submitted lots of BCG Vaccine to the Bureau of Biologics for release have demonstrated at least a 90-percent conversion rate with a high degree of consistency. Thus, the higher test dose is not required to achieve at least a 90-percent conversion rate. In addition, the lower test dose of 5 to 10 TU is a more sensitive indicator and therefore provides a better evaluation of the effectiveness of the BCG Vaccine. When the test dose is increased, the likelihood of detecting sensitivity induced by other mycobacteria is also increased. Accordingly, the comment is rejected. However, to provide greater flexibility for determining tuberculin reactivity, the Commissioner is revising the designated test dose from 5 or 10 TU to no more than 10 U.S. TU.

4. Two comments on proposed § 620.40(b)(4) suggested that the number of test subjects for testing the primary seed lot of vaccines be reduced from the proposed 200 to 100 tuberculin-negative persons. One comment stated that this reduction will not significantly change the validity of the test. The other comment stated that the WHO report, Part B, 3 recommends that a least 100 tuberculin-negative persons be tested and that such a study be made at regular intervals on some of the lots prepared, but not for every seed lot.

The Commissioner points out that the second comment misinterpreted the WHO report, Part B, 3, by applying it to a "seed lot" instead of a "vaccine lot." Part B, 3 recommends that such studies be made at regular intervals on some of the vaccine lots prepared. The difference in interpretation of the terminology used in the WHO report and the terminology used in the additional standards was discussed in paragraph 1 of this preamble. Rather than relying heavily on

tests of each lot of BCG Vaccine in final containers, as is done under the existing minimum requirements, the Commissioner proposed that 200 tuberculin-negative persons be selected to test the primary seed lot for its ability to induce sensitivity and to provide additional clinical evidence of safety. However, the Commissioner has become aware of the time and effort required and the increasing difficulty in recruiting volunteers for clinical trials. In view of the additional clinical requirements and safety data obtained on primary and secondary seed material, the Commissioner concludes that tests with at least 100 persons will provide the necessary assurance that the product is able to convert tuberculin-negative persons to tuberculin sensitivity without unexpected untoward reactions. Accordingly, the comments are accepted, and § 620.40(b)(4) is amended to require that at least 100 tuberculin-negative persons be selected to test the primary seed lot.

ESTABLISHMENT AND PERSONNEL REQUIREMENTS

5. One comment on proposed § 620.41(a) (21 CFR 620.41(a)) stated that it may be impossible to have a separate water supply and sewage disposal system for the BCG unit.

The intent of the proposed isolation of the BCG unit was to prevent contamination of the BCG Vaccine with extraneous organisms. However, the Commissioner has concluded that an absolute requirement for a separate water and sewage system may be extremely difficult to achieve. Accordingly, the comment is accepted, and § 620.41(a) is amended in the final regulation to require that the facilities for water supply and sewage and trash disposal be designed in a manner that prevents contamination of the BCG unit.

6. One comment on proposed § 620.41(a) stated that the requirement for a separate area for all control testing in which contaminating microorganisms may be cultured or in which animals are used implies that the culturing for sterility tests must be done in a separate BCG unit. The comment suggested that it is enough that these tests be conducted in rooms separated from production and cultivation.

The Commissioner agrees that culturing or incubation of sterility tests must be done in rooms separate from BCG production. Moreover, these rooms must be in an area physically separated from the BCG unit to prevent contamination of the BCG Vaccine with extraneous microoganisms that may appear in cultures during sterility testing. To clarify use of the phrase "BCG unit," § 620.41(a) is amended in the final regulations to define a BCG unit as the space used for storage of primary and secondary seed cultures and for vaccine preparation, including culture maintenance, media inoculation for propagation, harvesting, filling into final containers, sealing of final containers, media production, and cleaning and sterilization of glassware. The space used for incubation of bulk and final container sterility tests, tests to determine the numbers of colony-forming units, animal tests, and necropsies are not part of the "BCG unit."

7. One comment on proposed § 620.41(b)(2) suggested an amendment to require the wearing of shoes for use only in the BCG unit.

The Commissioner believes the suggested amendment is not necessary because generally accepted industry practices, including the use of disposable protective footwear, adequately protect the product. Accordingly, the comment is rejected.

PRODUCTION

8. One comment on proposed § 620.42(a) (21 CFR 620.42(a)) suggested that only one passage is needed in seed buildup for the production of BCG Vaccine.

The Commissioner believes that the comment has misinterpreted the definition of the term "passage." Each transfer of inoculum, starting from the freeze-dried or frozen seed lot into a culture medium in a seed buildup, is a passage. It is impractical to produce BCG Vaccine after only one passage, as suggested by the comment, because several passages are required to reactivate the freeze-dried or frozen seed lot

and build up an adequate amount of material for the satisfactory production of a lot of BCG Vaccine. Accordingly, the comment is rejected.

9. The Commissioner recognizes that, to reduce the potential growth and proliferation of virulent mutants, it is important to restrict the total number of passages in relation to the time the organisms are actively growing. Proposed § 620.42(a) restricted the number of passages in seed buildup from secondary seed lot to a lot in final containers to 9 within a 6-month period. However, there was no restriction in the number of passages from primary seed lot to a lot in final containers in the event that a secondary seed lot was not used.

Therefore, the Commissioner is amending § 620.42(a) to specify that only 9 passages are permitted if the inoculum used for final container material is made from a primary rather than secondary seed lot. In addition, if a secondary seed lot is used, the number of passages from primary seed lot in the preparation of a secondary seed lot is restricted to 3 passages within a 2-month period of time.

10. One comment on proposed § 620.42(a) asked whether this provision applies to 9 inocula or 9 passages. The comment stated that 9 passages cannot be completed within the proposed 6-week period and suggested a change to a 6-month period.

The Commissioner intended to permit no more than 9 passages within a 6-month period, and § 620.42(a) of the final regulation is amended accordingly.

11. One comment on proposed § 620.42(c) stated that a determination of the number of colony-forming units (CFU) on liquid bulk BCG would be more uniform and representative of production than the proposed determination of CFU on 5 vials of BCG Vaccine before and after freeze-drying. The comment also requested clarification of whether the contents of the 5 vials could be pooled before determining the CFU.

The purpose of the testing prescribed in § 620.42(c) is to provide information on the loss of viability due to freeze-drying and on the uniformity of CFU as distributed into final containers. Testing of liquid bulk material or pooled vials does not provide information on the uniformity of CFU in final containers. For this reason, the test must be conducted on the contents of individual final containers. For clarification, § 620.42(c) of the final regulation is amended to specify that CFU shall be determined on the contents of individual final containers of BCG Vaccine from each lot both before and after freeze-drying. Correspondingly, § 620.44(a) (21 CFR 620.44(a)) is amended to require that the number of CFU be determined on the contents of each of at least 10 individual final containers of each lot of BCG Vaccine. Of the 10 or more individual final containers tested, at least 5 shall be tested before, and an equal number shall be tested after, freeze-drying.

Potency Tests

12. One comment on proposed § 620.44 suggested that this section should be entitled *Viability* rather than *Potency*, because the test for CFU determines the viability of the vaccine. The comment provided no documentation other than the statement that BCG Vaccine, as currently licensed, contains considerable portions of biologically active materials that are potentiated by the presence of viable BCG. This potentiation action is claimed to vary with different quantities of each of the factors in a nonlinear manner.

The Commissioner agrees that the test for CFU determines the viability of BCG in the vaccine. However, viability is related to potency. Loss of viability results in a loss of potency. Section 600.3(s) (21 CFR 600.3(s)) interprets "potency" as "the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result." Thus, viability of the organisms is only one of several criteria used to evaluate the ability of the BCG Vaccine to effect a given result. Accordingly, the test for CFU is included in the general category of "potency" as used in these regulations for all biological products, and

the comment is rejected. The commentor did not identify the portions of biologically active materials and did not submit data to establish in which way, or to what degree, these materials (presumably nonviable) affect or are affected by the viable portions of the vaccine in the prevention of tuberculosis. Therefore, the Commissioner is unable to address this issue and the comment is rejected.

13. One comment on proposed § 620.44(a) recommended using Lowenstein's medium, rather than Youman's medium as specified in the proposal, for determining the number of CFU.

The Commissioner is aware that a number of equally reliable methods employing a variety of growth-promoting media are used to determine the number of CFU. The Bureau of Biologics has had many years of experience with the test defined in § 620.44(a) and has found the test using Youman's medium to be simple, direct, and reliable. By using one method rather than establishing a separate test method for each manufacturer's product, the Bureau is better able to compare products from all manufacturers. If a manufacturer wishes to use another method and presents evidence in writing to the Director, Bureau of Biologics, demonstrating that the modification will provide assurances that are equal to, or greater than, the assurances provided by the standards specified in the regulations, the Director, Bureau of Biologics, may accept the equivalent methods and send written approval of the modification. To accommodate this procedure, the final regulations are amended by adding a new § 620.49 *Equivalent methods* (21 CFR 620.49) to provide flexibility and encourage the development and use of manufacturing and test procedures that may be better than those currently available. However, the Bureau will continue its parallel testing using Youman's medium.

14. One comment on proposed § 620.44(a) recommended using 1.9 percent sodium glutamate to reconstitute the freeze-dried vaccine in final containers and incubating the reconstituted vaccine for 2 hours before proceeding with the test for CFU. The comment said at least a 1-log increase in viable CFU was obtained by this method.

The purpose of the test prescribed in § 620.44(a) is to measure the potency of each lot as it will be administered to humans. Because the diluents now used to reconstitute BCG Vaccine prior to injection are not known to enhance the viability of the organisms; the procedures suggested by the comment would produce artificially high test values not representative of the vaccine administered to humans. Accordingly, the comment is rejected. However, § 620.44(a) is amended to make clear that potency testing must be conducted on vaccine that has been reconstituted as for human use with the diluent recommended by the manufacturer.

15. One comment on proposed § 620.44(a)(1) provided data and suggested that the test for CFU can be performed more easily, without loss in reliability, by first making serial log dilutions of an appropriate volume of reconstituted vaccine up to a point where serial half-log dilutions will result in at least one tube containing between 10 and 50 CFU. The comment

stated that the test for CFU performed by conducting serial half-log dilutions throughout, as proposed, wastes labor and material. Another comment stated that the proposed volume of 1.4 milliliters (ml) for serial transfer in making half-log dilutions was incorrect.

The Commissioner concludes that data submitted support the suggested change that the initial dilutions can be made as log dilutions. The test procedure in § 620.44(a)(1) through (4) is reorganized and amended, and the suggested change appears in paragraph (a)(1) of that section. The 1.4 milliliters for serial transfer in making half-log dilutions was in error. The corrected volume, 2.0 ml for transfer in making half-log dilutions, appears in § 620.44(a)(2) in the final regulation.

16. One comment on proposed § 620.44(b) suggested that the minimum weight for guinea pigs for use in the potency test should be changed from at least 300 grams (g) to at least 250 g. The comment stated that

guinea pigs in the 250 to 300 g range have been used over the years and have produced satisfactory results.

The Commissioner advises that the minimum weight of 300 g was proposed because a certain degree of maturity of the guinea pigs is necessary to assure reliable responses to the vaccine. However, a recent review of protocols submitted by manufacturers demonstrates that guinea pigs weighing no less than 250 g have the necessary degree of immunologic maturity. Accordingly, the comment is accepted, and § 620.44(b) of the final regulation is amended to provide for a weight of no less than 250 g.

17. One comment on proposed § 620.44(b)(1) suggested that the intradermal guinea pig test could be conducted by administering a drop of vaccine on the skin of the guinea pig and puncturing the skin through the drop of vaccine, rather than by injecting intradermally graded dilutions of the vaccine with a specified volume.

The Commissioner advises that intradermal injections of graded dilutions of the vaccine with a specified volume result in animal responses to the various dilutions. If the vaccine is administered as suggested by the comment, the amount or volume of the vaccine administered will be variable and unknown, thereby precluding an estimation of the vaccine potency. Accordingly, the comment is rejected.

18. One comment on proposed § 620.44(b)(2) suggested revision to permit the use of a test dose of BCG Vaccine containing a range of 1 to 33×10^5 CFU rather than the proposed range of 1 to 9×10^5 CFU.

The Commissioner advises that BCG Vaccine intended for percutaneous injection in humans contains a large number of CFU which, if injected undiluted intradermally into guinea pigs, would produce more extensive reactions than those prescribed in § 620.44(b)(3) and would make estimation of vaccine potency difficult. For this reason, the test dose of 0.1 ml of vaccine containing a range of only 1 to 9×10^5 CFU was chosen. However, review of protocols submitted by manufacturers demonstrates that the number of CFU required to produce the reactions prescribed in § 620.44(b)(3) may vary depending on the strain of organism used and/or the method of production. Accordingly, the comment is accepted and § 620.44(b)(2) of the final regulation is amended to specify that vaccine intended for percutaneous injection into humans must be reconstituted with the manufacturer's recommended diluent so that at least 1 estimated human dose (that may vary for each type of vaccine but is estimated to be within a range of 1 to 33×10^5 CFU) is contained in 0.1 ml. A narrower range of CFU is to be determined for each manufacturer's vaccine and specified in the license application. One-tenth ml of the selected dose of vaccine and 0.1 ml of each of 3 ten-fold dilutions (1:10, 1:100, and 1:1000) shall be injected into the guinea pigs. The diluent for the ten-fold dilutions shall be an isotonic solution for injection.

The Commissioner is also amending proposed § 620.44(b)(3)(i) to specify that observations of all 4 vaccination sites in the intradermal guinea pig tests be read on the same day. The time required for the organisms to grow in guinea pig intradermal tissue may vary, and therefore the flexible time period of 2 to 4 weeks after BCG vaccination is allowed. Because the test requires an essentially negative reaction in tests of the greatest dilution of BCG Vaccine and a maximum reaction of 4 to 10 millimeters (mm) in the greatest concentration of BCG Vaccine, the specification is added that all 4 vaccination sites be observed and read on the same day.

19. One comment on proposed § 620.44(b)(3)(ii) suggested that the degree of tuberculin sensitivity should be determined by measuring the amount of induration, which is the hardening of the skin resulting from inflammation, rather than by measuring the amount of erythematous reaction, which is the reddening of the skin resulting from inflammation, as proposed.

The Commissioner proposed that tuberculin sensitivity be measured by erythematous reaction because, in guinea pigs, redness of the skin is easier to measure, is usually coincident with induration, and is subject to less error than hardening of the skin

caused by inflammation and swelling. Accordingly, the comment is rejected.

20. The Commissioner is amending proposed § 620.44(b)(3)(iii) to clarify the time when the guinea pigs should be weighed. As amended, the final regulation now states that "at the end of the test period each guinea pig is weighed * * *."

21. The Commissioner is adding a new paragraph § 620.44(c) to the final regulations in response to a comment made in regard to § 620.40(b)(4) and discussed in part under paragraph 4 of this preamble. The comment pointed out that the WHO report, Part B, 3, recommends that studies in humans be made at regular intervals on some of the vaccine lots prepared to ensure that adequate control of BCG Vaccine has been achieved. The comment misinterpreted the WHO report by applying it to a "seed lot" instead of a "vaccine lot." However, the comment claimed that clinical testing of every lot of BCG Vaccine in a minimum of 10 persons had served very well.

The Commissioner rejects the comment's recommendation to test every lot of BCG Vaccine in a minimum of 10 persons because the increased testing requirements of the primary and secondary seed lots make the testing of every lot of BCG Vaccine unnecessary. The controlled number of passages in the time periods specified reduces the chance for mutation to virulent organisms. However, as a continuing check on the potency, safety, and efficacy of the BCG Vaccine in humans, the Commissioner is accepting the recommendation of the WHO report by adding a new paragraph (c) to § 620.44 to require that at least once annually, no less than one lot of BCG Vaccine that has satisfied all requirements and has been released by the Bureau of Biologics be tested for its ability to induce sensitivity in 20 tuberculin-negative people. In addition, the results of these tests are to be sent to the Director, Bureau of Biologics, as they are completed.

Test for Freedom From Virulent Mycobacteria

22. One comment on proposed § 620.45(a) (21 CFR 620.45(a)) suggested that animals used in the test for virulent mycobacteria should be observed for 3 months instead of the proposed 6 weeks. No data accompanied the comment to support an observation period of 3 months.

The Commissioner advises that data in protocols submitted by manufacturers demonstrate that an observation period of 6 weeks provides an adequate basis to determine that each lot of vaccine produced in accordance with these additional standards remains free from virulent mycobacteria. In addition, the Commissioner concludes

that an observation period of 3 months, as suggested by the comment, is unnecessarily restrictive because it impedes release of the lot and shortens its availability within the dating periods prescribed in § 610.53 (21 CFR 610.53). Accordingly, the comment is rejected.

General Requirements and Labeling

23. One comment on proposed § 620.46(b) (21 CFR 620.46(b)) asked whether a new date of manufacture could be established any time a determination for the number of CFU shows that the loss in viability (potency) has not exceeded 90 percent.

The Commissioner advises that a new date of manufacture may be established by a manufacturer only under the following conditions: (1) The product has not left the control of the licensed manufacturer; (2) the integrity of the product has not been compromised; (3) the product is retested and conforms to the requirements prescribed in §§ 610.13(a) (21 CFR 610.13(a)) and 620.44(b); (4) samples and protocols are submitted to the Director, Bureau of Biologics; and (5) the product is not issued by the manufacturer until written notification of official release is received from the Director, Bureau of Biologics, as required by § 620.48 (21 CFR 620.48). Section 620.46(b) of the final regulation is amended to specify that the date of manufacture is to be the date of initiation of the last valid determination for CFU after freeze-drying.

24. One comment on proposed § 620.46(b) requested revision of the date of manufacture to permit the use

of a dating period that is approved in the product license application but different from that prescribed for BCG Vaccine in § 610.53.

The Commissioner advises that it is not necessary to revise the date of manufacture as proposed in § 620.46, because § 610.53 was amended in the FEDERAL REGISTER of January 31, 1978 (43 FR 4006) by adding a new paragraph (b) *Exemptions.* This paragraph provides for such exemptions or modifications of the dating period with the written approval of the Director, Bureau of Biologics, in the form of an approved license amendment.

25. One comment on proposed § 620.47(c) (21 CFR 620.47(c)) suggested that the vaccine should be administered within 4 hours, rather than within the proposed 8 hours, after reconstitution. The comment provided no data to justify a statement that vaccine administered within 4 hours after reconstitution has a higher viability count and is subject to less chance of contamination and exposure.

The Commissioner is not aware of any data to support a reduction of the time period from 8 hours to 4 hours. Furthermore, current available data related to use and clinical experience demonstrate that the product is safe and effective when administered within 8 hours under good medical practice. Accordingly, the comment is rejected.

SAMPLES

26. One comment on proposed § 620.48(a)(1) suggested that the sample to be submitted to the Director, Bureau of Biologics, need be only 20 ml rather than the proposed 40 ml.

The 40-ml sample was proposed to ensure an adequate volume of product for all required tests, particularly when repeat tests are needed. However, the Commissioner has reconsidered this requirement and finds that 20 ml will generally be adequate because additional samples can be requested if and when needed. Accordingly, the comment is accepted, and § 620.48(a)(1) of the final regulation is amended to provide for at least 20 ml of sample.

27. In connection with proposed § 620.48(b), the Commissioner notes that the Bureau of Biologics has routinely informed manufacturers by telephone that a lot of vaccine has been released after the official release is signed by the Director of the Bureau or the Director's designated agent. However, this telephone communication has been misunderstood as constituting the notification of official release. The Commissioner advises that official notification means that the written release form has been received by the manufacturer. Accordingly, § 620.48(b) of the final regulation is amended to specify that BCG Vaccine is not to be issued by the manufacturer until written notification of official release is received from the Director, Bureau of Biologics.

The Commissioner has carefully considered the environmental effects of this regulation and, because the action will not significantly affect the quality of the human environment, has concluded that an environmental impact statement is not required. A copy of the environmental impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Therefore, under the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)) and under authority delegated to the Commissioner (21 CFR 5.1), Part 620 is amended by adding new Subpart E, consisting of new §§ 620.40 through 620.49 to read as follows:

* * * * *

Part 620

§ 620.40
§ 620.41
§ 620.42
§ 620.43
§ 620.44
§ 620.45
§ 620.46
§ 620.47
§ 620.48
§ 620.49

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[FR Doc. 79-7487 Filed 3-12-79; 8:45 am]

35.—Mumps Virus Vaccine, Live

† 35.3 Notice—May 16, 1978

– 43 FR 21052 –

[Docket No. 78N–0084]

MUMPS VACCINE AND MUMPS VIRUS VACCINE, LIVE

Immunization of Source Plasma (Human) Donors

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The Commissioner of Food and Drugs announces that (1) the manufacture of licensed Mumps Vaccine (prepared from killed mumps virus) has been discontinued and the product is no longer available for hyperimmunization of Source Plasma (Human) donors, and (2) the use of Mumps Virus Vaccine, Live (prepared from live, attenuated mumps virus) in place of Mumps Vaccine for hyperimmunization of Source Plasma (Human) donors is prohibited because available data do not support such use.

EFFECTIVE DATE: May 16, 1978.

FOR FURTHER INFORMATION CONTACT:

Michael L. Hooton, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20014, 301-443-1306.

SUPPLEMENTARY INFORMATION: Mumps Vaccine, Mumps Immune Globulin (Human) and Mumps Virus Vaccine, Live, are licensed biological products that are indicated for protection against mumps.

Mumps Vaccine also has been approved for the hyperimmunization of Source Plasma (Human) donors. Plasma from such donors is used for the manufacture of Mumps Immune Globulin (Human).

The Commissioner of Food and Drugs announces that (1) the manufacture of licensed Mumps Vaccine has been discontinued and the product is no longer available for hyperimmunization of Source Plasma (Human) donors; and (2) the use of Mumps Virus Vaccine, Live, in place of Mumps Vaccine for hyperimmunization of Source Plasma (Human) donors is prohibited.

Under § 601.25 (21 CFR 601.25) of the biologic regulations, the Panel on Review of Viral and Rickettsial Vaccines is evaluating the safety, effectiveness, and labeling of all Viral and Rickettsial Vaccines licensed before July 1, 1972. To date, the panel has determined that Mumps Vaccine is poorly antigenic and offers no sustained protection against mumps. Accordingly, the panel has recommended that licenses be revoked for the manufacture of Mumps Vaccine. There are only two licensed manufacturers of Mumps Vaccine in the United States, and both have discontinued manufacture of the vaccine. At one manufacturer's request, its license has been revoked. The dating period for the last lots of manufactured Mumps Vaccine expired in 1977, and therefore Mumps Vaccine is no longer available.

The Commissioner is aware of some uncertainty as to whether approval of Source Plasma (Human) licenses for immunization of donors with mumps vaccine includes immunizing donors with Mumps Virus Vaccine, Live (a live viral product).

The Commissioner finds that the available data do not support use of Mumps Virus Vaccine, Live for the hyperimmunization of Source Plasma (Human) donors. A specific product, Mumps Vaccine (a killed viral product), is the only licensed product that has been consistently approved for mumps hyperimmunization of Source Plasma (Human) donors.

Accordingly, Mumps Virus Vaccine, Live is prohibited for use to hyperimmunize Source Plasma (Human) donors. The Commissioner advises that the Food and Drug Administration will institute regulatory action against any Source Plasma (Human) establisnment which uses Mumps Virus Vaccine, Live to hyperimmunize Source Plasma (Human) donors.

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[FR Doc. 78-12185 Filed 5-15-78; 8:45 am]

X. Human Blood and Blood Products

	Page
B. Tests and Methods	281
5.— Blood Grouping Serum	281
†5.5 Final Regulation; Correction—May 9, 1978 (43 FR 19844)	597
10.— Blood Group Substances A, B, and AB	300
†10.2 Final Regulation—April 6, 1979 (44 FR 20673)	598
43.— Hepatitis B Surface Antigen	316
†43.3 Final Regulation—June 22, 1979 (44 FR 36381)	600
†43.4 Proposal—December 28, 1979 (44 FR 76811)	601
50.— Limulus Amebocyte Lysate	320
†50.4 Proposal—August 11, 1978 (43 FR 35731)	603
C. Anticoagulants	339
15.— Citrate Phosphate	339
†15.2 Final Regulation—August 4, 1978 (43 FR 34457)	606
†15.3 Proposal—January 15, 1980 (45 FR 2854)	609
D. Specific Additional Standards for Human Blood and Blood Products	342
15.— Platelet Concentrate	351
†15.5 Proposal—January 15, 1980 (45 FR 2852)	610
35.— Source Plasma	382
†35.9 Notice of Availability of Guideline—May 5, 1978 (43 FR 19461)	613
†35.10 Proposal—October 19, 1979 (44 FR 60332)	614
50.— Immune Serum Globulin	434
†50.3 Notice of Availability of Guidelines—April 14, 1978 (43 FR 15779)	615

B. Tests and Methods

5.—Blood Grouping Serum

†5.5 Final Regulation; Correction—May 9, 1978

– 43 FR 19844 –

[Docket No. 78N-0101]

PART 660—ADDITIONAL STANDARDS FOR DIAGNOSTIC SUBSTANCES FOR LABORATORY TESTS

Color Coding for Blood Grouping Serum; Correction

AGENCY: Food and Drug Administration.

ACTION: Final Rule; Correction.

SUMMARY: This rule corrects the biologics regulations to delete reference to the Standard Ink Book and provide that final container labels of blood grouping serum may be color coded with a visual match to a specific color sample designated by the Director, Bureau of Biologics. The Standard Ink Book, which was published by the Government Printing Office, is out of print, and the Commissioner of Food and Drugs is therefore approving, upon request, other coloring systems.

EFFECTIVE DATE: This document corrects regulations that become effective August 7, 1978.

ADDRESS: Written comments to the Hearing Clerk (HFC-20), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Al Rothschild, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20014, 301-443-1306.

SUPPLEMENTARY INFORMATION: In the FEDERAL REGISTER of October 7, 1977 (42 FR 54534), the Commissioner of Food and Drugs published additional standards for the manufacture of blood grouping serum (21 CFR 660.20 through 660.29). Section 660.28(a)(1) of these standards requires that the final container label of all blood grouping sera be completely white, except that all or a portion of the final container label of certain specified antisera may be color coded with a visual match of the specific color samples identified in § 660.28(a)(1) and

– 19845 –

contained in the Standard Ink Book sold by the Superintendent of Documents, U.S. Government Printing Office. The additional standards became effective April 6, 1978, except that the effective date for the labeling regulation is August 7, 1978.

It has come to the attention of the Commissioner that the U.S. Government Printing Office has discontinued publication of the Standard Ink Book. Consequently, the book is unavailable

for manufacturers to match visually the color for final container labels with the color designated in the regulation.

The Director, Bureau of Biologics, has selected, from another coloring system readily available to printers, colors that are visual matches or similar to the colors designated in the Standard Ink Book. A memorandum identifying the coloring system and the colors has been sent to all licensed manufacturers of blood grouping serum. It is available to all other interested persons upon request from the Hearing Clerk (HFC-20), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857. Colors in other coloring systems will be visually matched and identified upon request and submission of the coloring system to the Director, Bureau of Biologics.

Accordingly, the Commissioner is amending § 660.28 in paragraph (a)(1) to delete reference to the Standard Ink Book and to provide that final container labels of the antisera specified in § 660.28(a)(1) may be color coded with a visual match to specific colors designated by the Director, Bureau of Biologics.

Therefore, under the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)) and under authority delegated to the Commissioner (21 CFR 5.1), § 660.28(a)(1) is revised to read as follows:

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§ 660.28

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[FR Doc. 78-12512 Filed 5-8-78; 8:45 am]

10.—Blood Group Substances A, B, and AB

†10.2 Final Regulation—April 6, 1979

– 44 FR 20673 –

[Docket No. 77N-0438]

PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

PART 680—ADDITIONAL STANDARDS FOR MISCELLANEOUS PRODUCTS

Blood Group Substances A, B, and AB; Additional Standards

AGENCY: Food and Drug Administration.

ACTION: Final Rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the biologics regulations to prescribe additional standards to ensure safety, purity, potency, and effectiveness in the manufacture of Blood Group Substances A, B, and AB.

DATES: Effective April 6, 1979, except the labeling requirements, which become effective October 3, 1979.

FOR FURTHER INFORMATION CONTACT: Michael L. Hooton, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20014, 301-443-1306.

SUPPLEMENTARY INFORMATION: Blood Group Substances A and B are preparations of swine (porcine) and horse (equine) gastric mucins, respectively, and are used as immunogens in the production of commercial diagnostic reagents. The gastric mucins of horses may also contain group A activity. If the antigenicity of group A substance from horses equals or exceeds the potency requirements for group A substance, the material is identified as Blood Group Substance AB. The diagnostic reagents manufactured from blood obtained from individuals immunized with Blood Group Substances are used for ABO grouping procedures.

In the FEDERAL REGISTER of March 21, 1978 (43 FR 11716), the Food and Drug Administration (FDA) proposed to amend the biologics regulations in Part 680 (21 CFR Part 680) by adding seven new sections, §§ 680.20 through 680.26, that prescribe additional standards for the manufacture of Blood Group Substances. The agency also proposed to amend § 610.53(a) (21 CFR 610.53(a)) to change the proper name of the products in conformity with current usage.

Interested persons were given until May 22, 1978 to submit written comments. Two letters concerning the proposal were received. The comments contained in the letters and the agency's responses follow:

One comment on proposed 0.22(g)(1)(iv) recommended that m temperature be defined as 15° to C, in conformity with U.S.P. specitions, rather than 20° to 24° C as posed.

DA advises that the potency and ntity testing proposed under 30.22 is performed with diagnostic i-A and anti-B Blood Grouping ums. These reagents perform effecly only within a narrow temperae range. Therefore, the 20° to 24° C it is established to ensure that the uired test is accurate. This temature range differs from that preibed for drugs in the U.S.P. because the unique temperature requirents of the diagnostic reagents inved. Accordingly, the comment is ected.

2. One comment on proposed 80.23(d)(1) recommended that the munizing dose for the anaphylactic st be the contents of a final containrather than 1.0 milliliter (ml).

FDA recognizes that a single immuzing dose (final container content) the product may vary from 0.5 to ml. Because the anaphylactic test performed to evaluate any possible zard associated with a single immuzing dose of the product, a predeterined test volume may not be appropiate. Accordingly, the comment is cepted and § 680.23(d)(1) is amended the final rule to provide that

he contents of a final container be inected into each of the guinea pigs.

3. One comment on proposed 680.24(c) recommended that the reglations permit the use of phenol as a reservative. The comment suggested hat a preservative would facilitate he processing and packaging of the roduct.

The agency is aware that phenol is ormally used as an extracting reagent n the manufacture of Blood Group Substances and that the finished prodict may contain traces of phenol. However, following manufacture, sterle Blood Group Substances are very table and require no further addition of preservatives. Accordingly, the gency is amending § 680.24(c) in the inal rule to recognize that phenol may be present in Blood Group Substances as a residual from manufacturing. The addition of any preservative remains prohibited.

4. One comment on the labeling requirements of § 680.25 suggested that because the dry weight concentration of Blood Group Substances per unit volume is often irrelevant to the biologic activity of the product, the proposal to label the product in terms of dry weight will not contribute to the safety or efficacy of the product. Including dry weight information would also require label changes from lot to lot.

The agency accepts the comment. In addition, it is noted that the required safety, anaphylaxis, and pyrogen tests are performed on the contents of final containers, rather than on the dry weight of product. Accordingly, §§ 680.24(d) and 680.25 (a) and (c) are amended to reference the contents of a final container of the product in terms of an immunizing dose rather than in terms of dry weight to volume.

5. One comment on proposed § 680.25 (a) and (b) suggested that the information required on each final container label is excessive because of the limited label space.

The agency recognizes that the container label may be too small to accommodate legibly all of the information required under proposed § 680.25 (a) and (b). Accordingly, § 680.25 is amended in the final rule by revising paragraph (a) to reduce the number of items required on the final container label and paragraph (b) to require that, if the final container is not enclosed in a package, e.g., the container is enclosed only in an unlabeled shipping carton, all information required for the package label in paragraph (c) of this section shall accompany and be attached to each final container.

6. Two comments on proposed § 680.26(a) suggested that the number of final containers (70) to be submitted for release testing is unnecessarily large. One of the comments recommended that the requirement should be 30 final containers.

The agency has considered the amount of material needed for adequate potency and identity, safety, sterility, pyrogen, and anaphylaxis test-

ing. Although 30 final containers may be inadequate, the agency believes that the volume of product contained in 40 final containers will be sufficient. Accordingly, the comments suggesting that fewer final containers be submitted for release testing are accepted and § 680.26(a) is amended in the final rule by requiring 40 final containers.

Therefore, under the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1), Parts 610 and 680 are amended as follows:

* * * * *

§ 610.53

Part 680

§ 680.20
§ 680.21
§ 680.22
§ 680.23
§ 680.24
§ 680.25
§ 680.26

* * * * *

[FR Doc. 79-10714 Filed 4-5-79; 8:45 am]

43.—Hepatitis B Surface Antigen

†43.3 Final Regulation—June 22, 1979

– 44 FR 36381 –

PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

PART 660—ADDITIONAL STANDARDS FOR DIAGNOSTIC SUBSTANCES FOR LABORATORY TESTS

Biological Products Standards; Additional Standards for Hepatitis B Surface Antigen

AGENCY: Food and Drug Administration.

ACTION: Final Rule.

SUMMARY: This document amends the biologics regulations to prescribe standards for the manufacture of Hepatitis B Surface Antigen (HBsAg).

EFFECTIVE DATE: July 23, 1979; labeling requirements shall be effective December 19, 1979.

ADDRESS: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Michael L. Hooton, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20205, 301-443-1306.

SUPPLEMENTARY INFORMATION: A notice of proposed rulemaking was published in the FEDERAL REGISTER of October 7, 1975 (40 FR 46318), in which the Food and Drug Administration (FDA) proposed to amend the biologics regulations by adding additional standards, §§ 660.40 through 660.46, governing the manufacture of Hepatitis B Surface Antigen (HBsAg). Hepatitis B Surface Antigen is the surface component of hepatitis B virus. The virus is responsible for causing type B viral hepatitis in patients receiving transfusions of blood which contain HBsAg, and from injection with devices and products contaminated with this virus. Anti-HBs appears in the serum of individuals having recovered from type B virus infection. The disease is unlikely to recur in previously infected individuals who have anti-HBs.

Hepatitis B Surface Antigen may be used as an in vitro diagnostic reagent to determine the presence of anti-HBs in the serum of individuals who have recovered from type B infection. The product may also be used for standardization in the manufacture of Hepatitis B Immune Globulin (Human).

Four letters of comment were received in response to the proposal:

1. Two comments concerned the dating periods for HBsAg products in proposed § 610.53. The comments stated that certain products such as HBsAg, when coupled to cryopreserved red blood cells or aldehyde fixed red blood cells, are stable for periods of a year or more. The Comments requested that

– 36382 –

§ 610.53 be amended to included dating periods for these products.

Section 610.53 prescribes dating periods for licensed products only, and

there are no existing licenses or pending license applications for the products referenced by the comments. Section 610.53 will be amended if and when licenses are issued for the subject products in response to license applications. Accordingly, the comments are rejected.

2. One comment on proposed § 660.41 suggested that alternatives to heat treatment of products and ancillary reagents should be permitted as methods for reducing the risk of transmitting type B viral hepatitis.

The phrase "such as the heating of albumin and plasma protein fraction for 10 hours at 60° C" was not intended to limit the methods for reducing the risk of transmitting type B virus. Rather, the phrase was used as an example of one procedure currently considered satisfactory. To preclude further confusion, the "such as" phrase is being deleted from § 660.41(a) in the final regulation. However, it should be noted that the specific procedure for reducing the risk of transmitting type B virus infection must be described in the license application or its amendment and approved by the Bureau of Biologics.

3. Two comments on proposed § 660.45(a) objected to the requirement that the identification of any antigen subtype must appear on the final container and package labels of products which are not intended for epidemiological investigations.

The agency agrees that not every antigen subtype need be identified on the container and package labels. However, the designation of the "d and y" antigen subtype is necessary for all HBsAg products, regardless of their use, in order to better identify the product and to facilitate investigation of product deficiencies. Designation of the "r and w" antigen subtype is necessary to facilitate the product's definition only if the product is intended to identify the "r and w" antibody subtype. Accordingly, § 660.45(a) is amended in the final regulation to specify that the label bear the "d and y" antigen subtype and the source of the product, e.g., HBsAg/ad chimpanzee, and to provide that if the product is intended to identify antibodies to the "r and w" antigen subtype, the antigen subtype designation shall include the "r and w" antigen subtype, e.g., HBsAg/adw chimpanzee.

4. The first sentence of the labeling section of the proposal erroneously cited § 320.10. This is corrected to read "In addition to the requirements of §§ 610.60, 610.61, and 809.10 * * *."

Therefore, under the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)) and under authority delegated to him (21 CFR 5.1), the Commissioner of Food and Drugs is amending Parts 610 and 660 as follows:

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§ 610.53

Part 660

§ 660.40
§ 660.41
§ 660.42
§ 660.43
§ 660.44
§ 660.45
§ 660.46

* * * * *

[FR Doc. 79-19449 Filed 6-21-79; 8:45 am]

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†43.4 **Proposal—December 28, 1979**

– 44 FR 76811 –

[21 CFR Part 660]

[Docket No. 79N-0076]

Antibody to Hepatitis B Surface Antigen; Reduction in the Number of Samples Submitted

AGENCY: Food and Drug Administration.

ACTION: Proposed Rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the biologics regulations reducing the number of samples of diagnostic test kits containing Antibody to Hepatitis B Surface Antigen iodinated with ^{125}I that must be submitted to FDA's Bureau of Biologics (the Bureau) for testing after licensure and official release of at least five consecutive lots of diagnostic test kits. Tests conducted by the Bureau show that it is no longer necessary to require sam-

ples from every lot of diagnostic test kits produced once a manufacturer is issued a license for the product and consistency in regular production is established.

DATE: Comments by February 26, 1980.

ADDRESS: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Richard E. Fisher, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20205, 301-443-1306.

SUPPLEMENTARY INFORMATION: Antibody to Hepatitis B Surface Antigen is a licensed diagnostic reagent used to detect Hepatitis B Surface Antigen in the serum of blood and plasma donors. A blood or plasma donor whose serum gives a positive reaction in a test with this diagnostic reagent is rejected from any further donations because the donor may be a potential carrier of viral hepatitis that can be transmitted by blood transfusion to a recipient or by the exposure of these contaminated products to their processors and other handlers. To reduce the risk of transmitting viral hepatitis through these human blood products, § 610.40 of the biologics regulations (21 CFR 610.40) requires that each donation of blood and plasma used in preparing a biological product be tested for the presence of Hepatitis B Surface Antigen. Only licensed Antibody to Hepatitis B Surface Antigen can be used in performing the tests. Section 610.40(b)(3) also requires

that testing be performed by the facility collecting the blood or by written agreement with a clinical laboratory meeting the standards of the Clinical Laboratories Improvement Act and qualified to perform radioimmunoassay or other acceptable third-generation sensitivity tests for the presence of Hepatitis B Surface Antigen. Both the clinical laboratories and the licensed manufacturers who do their own testing for hepatitis are required to participate in proficiency testing programs undertaken by the Bureau of Biologics (§ 610.40(e)).

The regulations governing the manufacture of Antibody to Hepatitis B Surface Antigen are prescribed in §§ 660.1 through 660.5 (21 CFR 660.1 through 660.5). Section 660.2(f)(2) provides that Antibody to Hepatitis B Surface Antigen that has been iodinated with ^{125}I may be issued by the manufacturer without obtaining an official release from the Director of the Bureau (the Director), provided the manufacturer submits a protocol of tests and a sample from each lot of the diagnostic test kit.

When a new product is being developed by a manufacturer, smaller lots or fewer lots are produced to avoid loss of valuable source material until specifications are established and the product is licensed. After licensing, production is increased to meet marketing needs. To assure the continuing quality and reliability of the product during this transition period, the license requires that manufacturers send samples of each lot of diagnostic test kits manufactured after licensing to the Bureau until the manufacturer has received written notification of official release of each of at least five consecutive lots of diagnostic test kits from the Director. Following written notification by the Director, subsequent lots of diagnostic test kits may then be released by the manufacturer as provided in § 660.2(f)(2) without obtaining official release, provided the manufacturer sends a protocol of tests and a sample of every lot of diagnostic test kits produced no more than 1 day following the manufacturer's release date. A written notification of official release is not required for all lots of diagnostic test kits manufactured because the product has a short dating period (shelf life) of 45 days.

During the past 3 years, there has been an increase in the number of manufacturers licensed for Antibody to Hepatitis B Surface Antigen iodinated with ^{125}I and a 50-percent increase in the number of samples of diagnostic test kits of this product received by the Bureau. As a result, the number of samples of diagnostic test

kits submitted now exceeds the number that can actually be tested. To determine the continued practicality of this sample submission procedure, the Bureau has evaluated the effectiveness of the product along with the testing capabilities of the licensed manufacturers or their testing laboratories by obtaining and reviewing data received from five hepatitis proficiency panels distributed from February 1975 through September 1977. The results of this review show that of the 1,164 establishments participating in the proficiency testing program, the rate of detecting hepatitis reactive samples (among coded negative and weakly reactive to strongly reactive samples) was 98.2 percent by radioimmunoassay.

The Bureau's experience in testing samples of lots of diagnostic test kits received and the satisfactory results of proficiency testing support the conclusion that it is unnecessary for manufacturers to send samples of every lot of diagnostic test kits produced after consistency in manufacturing has been established following licensing. A reduction in the number of samples of diagnostic test kits submitted thereafter would relieve an unnecessary burden on the manufacturers in loss of product and cost of mailing as well as a reduction in the cost of storing, testing, and disposing of samples of diagnostic test kits in the Bureau.

Accordingly, FDA proposed to amend § 660.2 by revising paragraph (f) to include provisions for retention samples of diagnostic test kits and adding a new § 660.6 *Samples, protocols, official release.* The current provisions of § 660.2(f)(1) concerning Antibody to Hepatitis B Surface Antigen not iodinated with ^{125}I are transferred to proposed § 660.6(a) and have been edited for consistency in format with paragraph (b). Proposed § 660.6(b) concerns Antibody to Hepatitis B Surface Antigen iodinated with ^{125}I and requires submission of one finished package of each lot of diagnostic test kits manufactured after licensing until written notification of official release is received for each of at least five consecutive lots. Each lot of diagnostic test kits must be withheld from distribution until such official release is received from the Director. After the manufacturer receives written notification that official release is no longer required, one finished package of a lot of diagnostic test kits must be submitted at periodic intervals of 90 days, and the manufacturer may release the product for distribution without obtaining official release. The lot of diagnostic test kits from which a sample is to be submitted must be the first one with the date of manufacture after the ninetieth day. Proposed § 660.6(b)(1)(ii) adds a requirement for sample submission of lots of diagnostic test kits if the Director finds that the product fails to maintain reliability in complying with the standards for this product. This action would be taken for the length of time necessary to reassure continuing reliability in compliance with the standards.

The agency has carefully considered the environmental effects of the proposed regulation and, because the proposed action will not significantly affect the quality of the human environment, has concluded that an environmental impact statement is not required. A copy of the environmental impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Therefore, under the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1), it is proposed that Part 660 be amended as follows:

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Part 660

§ 660.2
§ 660.6

* * * * *

[FR Doc. 79-39550 Filed 12-27-79; 8:45 am]

50.—Limulus Amebocyte Lysate

† 50.4 Proposal—August 11, 1978

– 43 FR 35731 –

[21 CFR Parts 610 and 660]

[Docket No. 78N-0171]

LIMULUS AMEBOCYTE LYSATE

Proposed Additional Standards

AGENCY: Food and Drug Administration.

ACTION: Proposed Rule.

SUMMARY: This document proposes additional standards for the manufacture of Limulus Amebocyte Lysate. This proposal is a republication and revision of an earlier proposal which is being revised in light of comments received and advances in technology and knowledge. This action being taken by the Food and Drug Administration (FDA) will give interested persons an opportunity to comment on the changes in the proposal.

DATES: Comments on or before October 10, 1978.

ADDRESS: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Michael L. Hooton, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20014, 301-443-1306.

SUPPLEMENTARY INFORMATION: The Commissioner of Food and Drugs is proposing to amend the biologics regulations to provide additional standards governing the manufacture of Limulus Amebocyte Lysate (LAL). LAL is prepared from the circulating blood cells (amebocytes) of the horseshoe crab (*Limulus polyphemus*). It is a recently licensed biological product used as a reagent in in vitro testing to detect bacterial endotoxins (pyrogens) in certain biological products and medical devices. Initial pyrogen testing by the Bureau of Biologics and published literature demonstrate that the LAL pyrogen test is more sensitive than the currently used classical rabbit pyrogen test in detecting endotoxins. In addition, the LAL test is more economical and requires a smaller volume of product for testing than the rabbit pyrogen test, and a large number of tests can be performed by one individual in 1 day.

In the FEDERAL REGISTER of November 4, 1977 (42 FR 57749), the Commissioner advised manufacturers of biological products that they must submit a license amendment for each product for which licensed LAL will be used in the official pyrogen test, and they must receive written approval of the amendment prior to such use of LAL. Proposed license amendments must include details of the test procedure and the criteria to be used in determining if a product passes or fails. If an amendment is approved, the LAL pyrogen test may be used in place of the rabbit test.

The Commissioner first proposed regulations in the FEDERAL REGISTER of September 18, 1973 (38 FR 26130) which governed the manufacture of LAL. Interested persons were given 60 days to file written comments. In response to these comments, substantial revisions of the 1973 proposed regulations have been made. In addition, these revised proposed regulations reflect advances in technology and knowledge since the first proposal. Accordingly, the Commissioner has determined that the proposed regulations be republished to provide interested persons an opportunity for comment. For the benefit of those who may wish to comment on this proposal, the Commissioner is identifying here only those changes in the new proposal which resulted from the substantive comments addressed to the 1973 proposal and the intervening advances in technology. Any literature or data upon which the Commissioner relies in this proposal may be seen in the Office of the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, between 9 a.m. and 4 p.m., Monday through Friday.

Shortly after publication of the proposed regulations under Part 273 (21 CFR Part 273), the biologics regulations were recodified and published in the FEDERAL REGISTER of November 20, 1973 (38 FR 32048) under Subchapter F, Parts 600 to 680 (21 CFR Parts 600 to 680). The new proposal reflects this recodification.

The Commissioner is proposing the following changes in the 1973 proposal:

1. Section 660.101 (formerly proposed § 273.5021) is being reproposed to require that a U.S. Reference Limulus Amebocyte Lysate preparation, obtained from the Bureau of Biologics, be used by the manufacturer to establish the sensitivity of LAL and to determine the suitability for release of each lot. This reference shall be used in addition to the U.S. Reference Endotoxin.

2. Section 660.102 (formerly proposed § 273.5022) is being reproposed to require new potency test procedures. Since publication of the 1973 proposal, production procedures have been modified to increase the sensitivity of LAL and decrease lot-to-lot variability. The Commissioner made available, in a notice published in the FEDERAL REGISTER of May 6, 1977 (42 FR 23167), a proposed guideline for establishing the sensitivity of each lot of LAL. The proposed guideline and the comments received concerning it form the basis for the potency test requirements under proposed § 660.102.

3. Section 660.103 (formerly proposed § 273.5023) is being reproposed to require that:

(a) There will be an adequate and available supply of source material, and to guarantee that the manufacture of LAL will not have an adverse impact on existing crab populations, the horseshoe crabs shall be returned alive to their natural environment after a single collection of their blood.

(b) The date of manufacture of each filling of each lot of LAL shall be the date the manufacturer initiated the last valid potency test for such filling.

(c) A sterility test be performed on each lot, unless a manufacturer presents data to the Director, Bureau of Biologics, demonstrating that sterility is not required for the product to perform reliably for its intended use.

(d) A test for quality be performed on each of 20 final containers from each filling or, if freeze-dried, from each filling in each drying chamber run. This quality control test is intended to eliminate false results due to extraneous contamination that may appear in the potency test prescribed in § 660.102.

4. Section 660.104 (formerly proposed § 273.5023(c)) is being reproposed to require that the geometric mean sensitivity, expressed as nanograms/milliliter (ng/ml) of the U.S. Reference Endotoxin and as determined by the potency test prescribed in proposed § 660.102, be included on the LAL final container label. The sensitivity of different lots of LAL may differ. To assure proper interpretation of results of tests performed with LAL, the sensitivity of the LAL reagent must be known. In addition, the use of only the most sensitive LAL may be necessary for testing some materials.

The Commissioner has carefully considered the environmental effects of the proposed regulation and, because the proposed action will not significantly affect the quality of the human environment, has concluded that an environmental impact statement is not required. A copy of the environmental impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Therefore, under the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)) and under authority delegated to him (21 CFR 5.1), the Commissioner proposes to amend Subchapter F in Chapter I of Title 21 of the Code of Federal Regulations as follows:

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§ 610.53

Part 660

§ 660.100
§ 660.101
§ 660.102
§ 660.103
§ 660.104
§ 660.105

* * * * *

[FR Doc. 78-22169 Filed 8-10-78; 8:45 am]

C. Anticoagulants

15.—Citrate Phosphate

† 15.2 Final Regulation—August 4, 1978

– 43 FR 34457 –

[Docket No. 77N-0352]

PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

PART 640—ADDITIONAL STANDARDS FOR HUMAN BLOOD AND BLOOD PRODUCTS

Anticoagulant Citrate Phosphate Dextrose Adenine Solution

AGENCY: Food and Drug Administration.

ACTION: Final Rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the whole blood (human) regulations to permit the use of the anticoagulant citrate phosphate dextrose adenine solution (CPDA-1) in whole blood (human) and certain products derived from whole blood (human), and to prescribe labeling for blood products that contain CPDA-1. When CPDA-1 is used as the anticoagulant, the storage period for whole blood (human) and red blood cells (human) may be extended from 21 to 35 days. In addition, the agency is amending other regulations concerning blood and blood products to facilitate the use of CPDA-1.

EFFECTIVE DATE: August 4, 1978.

FOR FURTHER INFORMATION CONTACT:

Michael L. Hooton, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20014, 301-443-1306.

SUPPLEMENTARY INFORMATION: The Commissioner of Food and Drugs

– 34458 –

is amending §§ 640.4(d) and 640.7(a) (21 CFR 640.4(d), 640.7(a)) to permit use of CPDA-1 in whole blood (human) and certain products derived therefrom, and to prescribe labeling for products containing CPDA-1. Consistent with this approved use of CPDA-1, the Commissioner is also amending the following related sections:

1. Section 610.53 (21 CFR 610.53), to permit a dating period of 35 days for whole blood (human) and red blood cells (human) collected and stored in CPDA-1 and to clarify the dating periods of single donor plasma (human) products.

2. Section 640.2 (21 CFR 640.2), to provide that the periodic check on sterile technique may be conducted between the 32d and 38th day after collection of blood in CPDA-1.

3. Section 640.4, to provide that when CPDA-1 is the anticoagulant, pilot samples for compatibility testing shall contain blood mixed with CPDA-1.

4. Section 640.16 (21 CFR 640.16), to provide that red blood cells (human) may be prepared within 35 days after whole blood is collected in CPDA-1.

5. Sections 640.22 and 640.32 (21 CFR 640.22, 640.32), to preclude use of whole blood (human) collected and stored in CPDA-1 as a source of platelet concentrate (human) and single donor plasma (human) platelet rich, respectively.

6. Section 640.34 (21 CFR 640.34), to extend by 14 days the time within which single donor plasma (human) and single donor plasma (human) liquid shall be separated from the red blood cells when CPDA-1 is the anticoagulant and to remove the restriction concerning the issuance of plasma for transfusion if there are more than 25 milligrams (mg) hemoglobin per 100 milliliters (ml) of plasma as determined by visual inspection.

Citrate phosphate dextrose (CPD) solution and anticoagulant citrate dextrose (ACD) solution are two anticoagulants authorized for use under § 640.4 for whole blood (human). The dating period prescribed under § 610.53 for whole blood (human) containing CPD or ACD and red blood cells (human) derived from whole blood (human) containing CPD or ACD is 21 days. Data demonstrate that whole blood (human) and red blood cells (human) stored in citrate anticoagulant supplemented with adenine for 35 days are as safe, pure, potent, and effective as if these blood products had been stored in citrate anticoagulant

without adenine for 21 days. In addition, except for platelet concentrate (human) for which data are lacking on the hemostatic effect, the data demonstrate that there are no differences in the yield, stability, safety, potency, and effectiveness of blood components and derivatives prepared from blood collected in anticoagulant supplemented with adenine and blood collected in anticoagulant without adenine.

Accordingly, in the FEDERAL REGISTER of January 20, 1978 (43 FR 2890), the Commissioner proposed to (1) authorize use of anticoagulant citrate phosphate dextrose adenine solution (CPDA) as an additional anticoagulant for whole blood (human), (2) provide a dating period of 35 days for whole blood (human) and red blood cells (human) collected and stored in CPDA, (3) prescribed labeling for the blood products containing CPDA, and (4) preclude use of whole blood (human) collected and stored in CPDA as a source of platelet concentrate (human).

Interested persons were given until March 21, 1978 to submit written comments. Twenty-one letters were received. Five letters expressed approval of the amendments as proposed. The comments contained in the remaining letters and the Commissioner's responses follow:

1. Four comments on the proposed amendment of § 610.53(a) recommended that the storage period for red blood cells (human) not be extended to 35 days. The comments stated that the published data adequately support a 35-day storage period for whole blood (human) but only marginally support the proposed 35-day storage period for red blood cells (human). One comment stated that CPDA should be used mainly to improve red blood cell quality (survival) rather than to extend the dating period to 35 days.

The Commissioner agrees that some published data (reference 46 of the proposal) demonstrate that the red blood cell post-transfusion survival of whole blood (human) stored in CPDA for 35 days is better than that of red blood cells (human) stored in CPDA for the same period. However, these data were considered at a public workshop on adenine sponsored by the Bureau of Biologics in conjunction with a meeting of the expert Panel on Review of Blood and Blood Derivatives (Ref. 36 of the proposal). Following extensive discussion by the Panel members and public participants, the Panel concluded that whole blood and red blood cells containing CPDA as the anticoagulant are safe and effective after 35 days storage. The Panel recommended that the Bureau of Biologics approve the use of CPDA as an anticoagulant and extend the dating period to 35 days for both products.

In addition, after publication of the proposal, data were submitted to the Bureau of Biologics on 15 units of red blood cells (human) having hematocrits of 75.7±3.4 percent (standard deviation) which were collected in CPDA and stored for 35 days. The average posttransfusion red blood cell survival of the 15 units was 77.6±7.0 percent (standard deviation) with 2 of the 15 units having red blood cell survivals of less than 70 percent. These additional data support the proposed 35-day storage period. The Commissioner concludes that whole blood (human) and red blood cells (human) stored in CPDA for 35 days are as safe, potent, and effective as the same products stored in citrate anticoagulant without adenine for 21 days, and that the quality of the red blood cells during the extended storage period is improved, an effect which becomes increasingly significant after about 10 days of storage. Accordingly, the comments are rejected and blood banks may use CPDA to improve red blood cell quality, to extend shelf life, or to accomplish both objectives.

2. One comment suggested that § 640.2(b) be amended to provide that the periodic check on sterile technique may be conducted between the 32d and 38th day after collection when CPDA is the anticoagulant. Another comment suggested that § 640.16(a) be amended to provide that red blood cells (human) may be prepared within 35 days after whole blood is collected in CPDA. One additional comment suggested amending § 610.53(a) to provide a dating period of 40 days for single donor plasma (human), liquid and § 640.34(a) and (c) to require that

single donor plasma (human) be separated from the red blood cells within 40 days after phlebotomy when CPDA is used as the anticoagulant.

Because CPDA extends the dating period for an additional 14 days, the Commissioner agrees that conforming amendments consistent with the extended dating period are necessary. Therefore, the comments are accepted and the periodic check on sterile technique, the separation of red blood cells (human) from whole blood, the separation of single donor plasma (human) from whole blood, and the dating period for single donor plasma (human), liquid under §§ 640.2(b), 640.16(a), 640.34(a) and (c), and 610.53(a), respectively are amended by adding a phrase which extends the time period 14 days when CPDA is used as the anticoagulant. In addition, the Commissioner is clarifying § 610.53(a) to identify the dating period of all single donor plasma products as the period from the date or time of collection of source blood.

3. One comment on the proposed amendment of § 640.4 requested that the regulations specify a range of concentration for dextrose and adenine.

The Commissioner advises that approval of CPDA is based on data supporting the specific formula identified

in the regulations. He is aware that the literature describes several other formulas for CPDA and encourages further development of data to establish optimal concentrations of dextrose and adenine, as well as of other additives. If and when additional data are submitted to support other formulations, the Commissioner will consider proposing their addition to the list of approved anticoagulants. Accordingly, the comment is rejected at this time.

4. One comment on the proposed amendment of § 640.4 suggested that CPDA-1, rather than CPDA, should be used as the abbreviation for the specific anticoagulant citrate phosphate dextrose adenine solution formula identified in the proposal. The comment stated that the literature already describes several variations of the proposed formula and that CPDA is not specific enough to identify the formula proposed.

The Commissioner agrees that "CPDA-1" is more specific than "CPDA" and will better identify the currently approved formula in the event that others are subsequently approved. Therefore, the comment is accepted and "CPDA-1" replaces "CPDA" in the appropriate sections.

5. One comment suggested that to insure the retention of red blood cell antigen reactivity for compatibility testing, § 640.4 should be amended to require that segments of the donor tubing contain anticoagulant.

The Commissioner agrees that anticoagulant is necessary to preserve red blood cell antigen reactivity for compatibility testing if the blood is to be stored for as long as 35 days. Accordingly, the comment is accepted and § 640.4 is amended by adding paragraph (g)(5) requiring that when CPDA-1 is used, pilot samples for compatibility testing shall contain blood mixed with CPDA-1.

In addition, data are currently available suggesting that samples of blood stored in citrate anticoagulant provide better preservation of red blood cell antigen reactivity for compatibility testing than do clotted samples of blood. For this reason, the Commissioner believes that all pilot samples for compatibility testing should be required to be collected and stored in citrate anticoagulant. The Commissioner intends to publish a notice of proposed rulemaking to provide all interested persons with an opportunity to comment on such a requirement.

6. Eight comments on the proposed amendment of § 640.22 recommended that the use of CPDA-1 in blood collected for the preparation of platelet concentrate (human) be approved as soon as data are available.

The Commissioner agrees, and when satisfactory data are received he will propose to provide for the manufacture of platelet concentrate (human) prepared from whole blood (human) collected in CPDA-1.

7. Consistent with the amendment of the regulations to preclude use of blood collected in CPDA-1 for preparation of platelet concentrate (human), the Commissioner is amend-

ing § 640.32(a) to provide that whole blood collected in CPDA-1 not be used for preparation of single donor plasma (human), platelet rich.

8. Four comments asked if single donor plasma (human), fresh frozen and antihemophilic factor (human) (AHF) may be prepared from blood collected in CPDA-1.

Blood collected in CPDA-1 may be used to prepare single donor plasma (human), fresh frozen and AHF. However, during a plasmapheresis procedure, there is no need for CPDA-1 in blood collection because the red blood cells are returned to the donor. Accordingly, single donor plasma products collected by plasmapheresis and source plasma (human) which may be used to prepare AHF must not contain CPDA-1.

9. One comment noted that § 640.34(g)(1)(iii) requires that the final single donor plasma product not be issued for transfusion if there are more than 25 mg hemoglobin per 100 ml of plasma as determined by visual inspection. The comment included data from studies that demonstrate that single donor plasma obtained from blood stored for 35 days in CPDA-1 may have plasma hemoglobin values greater than 25 mg hemoglobin per 100 ml of plasma. However, the data demonstrate that the greater hemoglobin levels have no clinical significance. The comment suggested that the restriction concerning 25 mg hemoglobin per 100 ml of plasma therefore be deleted from the regulations.

On the basis of data submitted and other relevant material, the Commissioner concludes that there is no adverse clinical significance from use of single donor plasma (human) products containing more than 25 mg hemoglobin per 100 ml of plasma in any of the approved anticoagulants, if the final product is inspected immediately after separation of the plasma as required in § 640.34 (g)(1)(i) and (g)(1)(ii). Therefore, the comment is accepted and §640.34 is amended by deleting paragraph (g)(1)(iii).

Therefore, under the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)) and under authority delegated to the Commissioner (21 CFR 5.1), Parts 610 and 640 of Subchapter F of Title 21 of the Code of Federal Regulations are amended as follows:

* * * * *

§ 610.53

Part 640

§ 640.2
§ 640.4
§ 640.7
§ 640.16
§ 640.22
§ 640.32
§ 640.34

* * * * *

[FR Doc. 78-21360 Filed 8-3-78; 8:45 am]

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†15.3 Proposal—January 15, 1980

– 45 FR 2854 –

[21 CFR PART 640]

[Docket No. 79N-0406]

Preparation of Platelet Concentrate (Human) and Single Donor Plasma (Human), Platelet Rich in CPDA-1; Removal of Restriction

AGENCY: Food and Drug Administration.

ACTION: Proposed Rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the biologics regulations to remove the restriction on the use of citrate phosphate dextrose adenine solution (CPDA-1) for a preparation of Platelet Concentrate (Human) and Single Donor Plasma (Human), Platelet Rich. This proposal is being made because there is satisfactory data to demonstrate that there are no differences in the yield, stability, safety, potency, and effectiveness of platelet concentrates prepared from blood collected in anticoagulant supplemented with adenine and blood collected in anticoagulant without adenine.

DATE: Written comments by March 17, 1980.

ADDRESS: Comments may be addressed to the Office of the Hearing Clerk (HFA-305), Food and Drug Ad-

ministration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Michael L. Hooton, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20205, 301-443-1306.

SUPPLEMENTARY INFORMATION: In the FEDERAL REGISTER of August 4, 1978 (43 FR 34457), FDA amended the biologics regulations to permit the use of citrate phosphate dextrose adenine solution (CPDA-1) as the anticoagulant in Whole Blood (Human) and certain products derived from Whole Blood (Human). When CPDA-1 is used as the anticoagulant, the storage period for Whole Blood (Human) and Red Blood Cells (Human), may be extended from 21 to 35 days.

At the time of publication of the August 4, 1978 final rule, satisfactory data were not available demonstrating the hemostatic effect of Platelet Concentrate (Human) prepared from blood collected in anticoagulant supplemented with adenine. Consequently, CPDA-1 was not authorized for use in Whole Blood (Human) intended for preparation of Platelet Concentrate (Human) or Single Donor Plasma (Human) Platelet Rich. In response to comments received on this proposed restriction, the Commissioner of Food and Drugs stated that "when satisfactory data are received he will propose to provide for the manufacture of Platelet Concentrate (Human) prepared from Whole Blood (Human) collected in CPDA-1" (43 FR 34459, item No. 6).

Since publication of the August 4, 1978 final rule, FDA has received satisfactory data that have been placed on file with the Hearing Clerk, Food and Drug Administration, and demonstrate that there are no differences in the yield, stability, safety, potency, and hemostatic efficacy in platelet concentrates prepared from blood collected in anticoagulant supplemented with adenine and blood collected in anticoagulant without adenine. Accordingly, FDA is proposing to remove the restriction for the use of CPDA-1 in the preparation of Platelet Concentrate (Human) and Single Donor Plasma (Human), Platelet Rich.

FDA advises that when the final rule of this proposal has been published, licensed blood establishments need not wait until notification of acceptance of appropriate license amendments to prepare Platelet Concentrate (Human) and Single Donor Plasma (Human), Platelet Rich from Whole Blood (Human) collected in CPDA-1. Submission of a label concurrent with the start of manufacture of Platelet Concentrate (Human), and Single Donor Plasma (Human), Platelet Rich in CPDA-1 will constitute an amendment to the license for those products.

FDA has carefully considered the environmental effects of the proposed regulation and, because the proposed action will not significantly affect the quality of the human environment, has concluded that an environmental impact statement is not required. A copy of the environmental impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Therefore, under the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)) and under authority delegated to him (21 CFR 5.1), the Commissioner of Food and Drugs proposes to amend Part 640 as follows:

* * * * *

Part 640

§ 640.22
§ 640.32

* * * * *

[FR Doc. 80-1275 Filed 1-14-80; 8:45 am]

D. Specific Additional Standards for Human Blood and Blood Products

15.—Platelet Concentrate

†15.5 Proposal—January 15, 1980

– 45 FR 2852 –

[21 CFR Parts 600, 610, and 640]

[Docket No. 79N-0405]

Platelet Concentrate (Human); Additional Standards

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the biologics regulations by: (1) deleting the volume limits for plasma needed for the shipping, processing, and storage of Platelet Concentrate (Human); (2) specifying that the Rh blood group designation as well as the ABO blood group designation be included in the labeling requirements of Platelet Concentrate (Human); and (3) reducing the dating period for Platelet Concentrate (Human) and Single Donor Plasma (Human), Platelet Rich stored at 1° to 6° C. This action is being taken to update the regulations concerning platelet products to reflect new scientific knowledge and experience.

DATE: Written comments by March 17, 1980.

ADDRESS: Written comments to the office of the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Robert J. Meyer, Bureau of Biologics (HFB-620), Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20205, 301-443-1306.

SUPPLEMENTARY INFORMATION: In the FEDERAL REGISTER of January 29, 1975 (40 FR 4300), FDA issued Additional Standards for Platelet Concentrate (Human) under §§ 640.20 through 640.26 (21 CFR 640.20 through 640.26). Section 640.24(d) (21 CFR 640.24(d)) requires that: (1) the volume of original plasma used for the resuspension of the platelets shall be determined by the storage temperature, so that it will maintain a pH of not less than 6 during the storage period; (2) the pH shall be measured on a sample of platelet concentrates that is at the selected storage temperature; and (3) one of the following storage temperatures and corresponding volume of resuspension plasma shall be used continuously: 20° to 24° C resuspended in 30 to 50 milliliters of plasma or 1° to 6° C resuspended in 20 to 30 milliliters of plasma. At the time of publication of the Additional Standards for Platelet Concentrate (Human), the available evidence demonstrated that these conditions of temperature, volume and pH were adequate to maintain the quality of the platelets at the concentrations that were attainable by existing manufacturing techniques.

Since the publication of the Additional Standards for Platelet Concentrate (Human), there have been significant changes in platelet production. At a public workshop held on January 5, 1978, representatives of industry and the Bureau of Biologics, Food and Drug Administration, met to evaluate the current methods of platelet production and to review current data so that the criteria of safety, purity, potency, and efficacy established by the regulations for Platelet Concentrate (Human) would remain consistent with the judgment of the scientific community. It was determined at this workshop that current manufacturing techniques are producing a higher concentration of platelets in each unit of Platelet Concentrate (Human) than was being produced when the existing platelet concentrate standards were promulgated. The effect of this change in platelet concentration is significant because the present upper limit of 50 milliliters for the volume of resuspension plasma for Platelet Concentrate (Human) in § 640.24(d) does not ensure the maintenance of the required pH of not less than 6 during the storage period. Indeed, in a separate study performed by the Bureau of Biologics from October 1, 1977 to December 31, 1978, 21 percent of the units of platelet concentrate submitted as prelicensing samples were found to have a pH value less than 6. Because pH is inversely correlated to the platelet concentration and platelet viability is known to be compromised at a pH of less than 6, FDA believes that current units of Platelet Concentrate (Human) with high platelet concentrations are likely to demonstrate a decrease in pH values due to inadequate plasma volumes and consequently become clinically ineffective. On the basis of published data and the results of the

study performed by the Bureau of Biologics, FDA concludes that the present limits for the volume of resuspension plasma for Platelet Concentrate (Human) does not ensure the quality of the product or encourage development of techniques that improve the yield of platelets from a unit of source blood. Therefore, FDA proposes to amend § 640.24(d) by deleting the volume limits of the resuspension plasma for Platelet Concentrate (Human) and to require that the volume of resuspension plasma be determined solely by the maintenance of a pH of not less than 6 during the storage period.

Consistent with the proposed changes in § 640.24(d) FDA proposes to amend § 640.20(a) (21 CFR 640.20(a)) by revising the wording concerning the volume of resuspension plasma in the definition of Platelet Concentrate (Human). Also, FDA proposes to amend § 600.15(a) (21 CFR 600.15(a)) and § 640.25(a) (21 CFR 640.25(a)) by deleting the references to the volume limits of the resuspension plasma for Platelet Concentrate (Human).

The biologics regulations also require in § 640.26(e) (21 CFR 640.26(e)) that the container label for Platelet Concentrate (Human) bear the blood group designations of the source blood. This requirement was established because FDA believes that labeling is an important factor in safely administering blood products. The user must be aware of the blood group designations so that platelets may be administered to recipients of the same blood group as the donor. Although tests to identify both the ABO and Rh blood groups are required for the blood from which plasma is separated for the preparation of Platelet Concentrate (Human), the labeling requirements concerning blood group designations for platelet products is interpreted by many people to include only the ABO blood group designation because of its clinical importance. However, platelet products are usually contaminated with significant numbers of red blood cells which can cause immunization to the Rh antigen. Therefore, FDA believes that in the interest of patient safety, the Rh blood group designation should also be clearly specified on the labeling of platelet products to provide clinicians additional information when avoidance of Rh sensitization is indicated. Accordingly, the agency proposes to amend § 640.26(e) (21 CFR 640.26(e)) by specifying that the container label for Platelet Concentrate (Human) bear the Rh blood group designation as well as the ABO blood group designation.

To ensure the safety, purity, potency and effectiveness of licensed biological

products, § 610.53 (21 CFR 610.53) specifies storage conditions and dating periods based upon clinical experience or laboratory tests within which licensed biological products are expected to be safe and yield their specific result. The present dating period for Platelet Concentrate (Human) and Single Donor Plasma (Human), Platelet Rich stored at 20° to 24° C or 1° to 6° C is 72 hours from the time of collection of the source blood. Published studies demonstrate that although the viability and function of platelets stored at either of the required storage temperature ranges for 48 hours are comparable, the platelets stored at 1° to 6° C for 72 hours are substantially and significantly inferior to platelets stored at 20° to 24° C for the same time period. Based on these published studies, FDA believes that the present 72-hour dating period for Platelet Concentrate (Human) and Single Donor Plasma (Human), Platelet Rich stored at 1° to 6° C is resulting in a product having inferior clinical efficacy. Therefore, FDA proposes to amend § 610.53(a) (21 CFR 610.53(a)) by changing the dating period for Platelet Concentrate (Human) and Single Donor Plasma (Human), Platelet Rich stored at 1° to 6° C from 72 hours to 48 hours from the time of collection of the source blood.

Consistent with these proposed changes in § 610.53(a), FDA proposes to amend § 640.25(b) (21 CFR 640.25(b)) by specifying that quality control testing be performed at the end of the storage period.

Pertinent background data on which the agency relies in proposing these amendments are on public display in

he office of the Hearing Clerk, Food nd Drug Administration, Rm. 4-65, 600 Fishers Lane, Rockville, MD 0857.

FDA has carefully considered the nvironmental effects of the proposed egulation and, because the proposed ction will not significantly affect the uality of the human environment, has oncluded that an environmental mpact statement is not required. A opy of the environmental impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Therefore, under provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, and 371, 52 Stat. 1041-1042 as amended, 52 Stat. 1050, 52 Stat. 1055-1056 as amended (21 U.S.C. 321, 352, and 371)) and the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1), it is proposed that Subchapter F of Title 21 of the Code of Federal Regulations be amended as follows:

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§ 600.15

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§ 610.53

Part 640

§ 640.20
§ 640.24
§ 640.25
§ 640.26

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[FR Doc. 80-1272 Filed 1-14-80; 8:45 am]

35.—Source Plasma

†35.9 Notice of Availability of Guideline—May 5, 1978

- 43 FR 19461 -

[Docket No. 78D-0099]

SOURCE PLASMA (HUMAN)

Availability of Guideline

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: This document announces the availability of a revised guideline for red blood cell immunization of Source Plasma (Human) donors. The agency has revised the guideline in response to manufacturers' comments that the guideline as initially issued was difficult to follow.

DATE: Written comments by June 5, 1978.

ADDRESS: Written comments and requests for copies of the guideline should be forwarded to the Hearing Clerk (HFC-20), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Joe K. Holloway, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20014, 301-443-1306.

SUPPLEMENTARY INFORMATION: The Commissioner of Food and Drugs issued a notice published in the FEDERAL REGISTER of May 17, 1977 (42 FR 25381) advising manufacturers of the availability of a guideline for immunizing Source Plasma (Human) donors with Red Blood Cells (Human). He hereby gives notice that the guideline referred to in the May 1977 notice has been revised and updated and is now on display at the office of the Hearing Clerk (HFC-20), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

The Food and Drug Administration (FDA) committee on red blood cell immunization found, through discussions and correspondence with the blood manufacturing industry, that the Bureau's current guideline, displayed May 1977 at the Hearing Clerk's Office, required revision and updating. Problems with the current guideline are that manufacturers found it difficult to (1) successfully immunize the donors at the recommended dosage and administering intervals, especially for *de novo* (initial) immunization, and (2) adequately match the donor's blood with the recipient's blood using the recommended criteria. The revised guideline will alleviate these problems.

Interested persons may obtain copies of the guideline by contacting the

office of the Hearing Clerk and identifying the guideline with the Hearing Clerk docket number found in brackets in the heading of this document.

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[FR Doc. 78-12258 Filed 5-4-78; 8:45 am]

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†35.10 Proposal—October 19, 1979

- 44 FR 60332 -

[21 CFR Part 640]

[Docket No. 79N-0117]

Source Plasma (Human); Amendment of Storage Temperature Requirements

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the storage temperature requirements for Source Plasma (Human) intended for manufacture into injectable products to permit one inadvertent exposure of the product to a temperature range of −20° to −5° C for no more than 72 hours, without requiring relabeling of the frozen product from "Source Plasma (Human)" to "Source Plasma (Human) Salvaged." Data submitted to the agency demonstrate the satisfactory recovery of clotting factor concentrates from the plasma despite the temporary elevation of storage temperature.

DATE: Comments by December 18, 1979.

ADDRESS: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Donna C. Williams, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20205, 301-443-1306.

SUPPLEMENTARY INFORMATION: Section 640.69(b) (21 CFR 640.69(b)) of the biologics regulations requires that, immediately after filling, Source Plasma (Human) intended for manufacturing into injectable products be stored at a temperature not warmer than −20° C. Such cold storage assures preservation of the antihemophilic factor in Source Plasma (Human). Source Plasma (Human) is fractionated into injectable plasma derivatives including clotting factors such as Antihemophilic Factor (Human) and Factor IX Complex (Human) used for treatment of patients with clotting factor deficiencies. Section 640.76(a) (21 CFR 640.76(a)) requires that Source Plasma (Human) intended for manufacture into injectable products that is inadvertently exposed to a storage temperature warmer than −20° C but colder than 10° C may be issued only if labeled as "Source Plasma (Human) Salvaged." This revised labeling provides the manufacturer of the fractionated plasma derivatives with important information concerning possible adverse effects on the clotting factors because of the inadvertent storage of the Source Plasma (Human) at temperatures warmer than −20° C.

By letter dated January 5, 1978, the Director of Regulatory Affairs and Clinical Development of Hyland Division Travenol Laboratories, Inc. on behalf of the Biological Section of the Pharmaceutical Manufacturers Association (PMA) requested the amendment of the Source Plasma (Human) regulations to allow for an inadvertent rise in storage temperature to not warmer than −5° C. for a time period not to exceed 72 hours during an unforeseen occurrence in spite of compliance with good manufacturing practices (e.g., freezer malfunction or power failure) without requiring such plasma to be relabeled "Source Plasma (Human) Salvaged." Data submitted in support of this request demonstrate that suitable potency levels of Antihemophilic Factor (Human) and Factor IX Complex (Human) were obtained from pools of plasma that contained Source Plasma (Human) Salvaged (stored at temperatures colder than 0° C) and Source Plasma (Human). Copies of the PMA request and supporting data are on file at the office of the Hearing Clerk (HFA-305), Rm. 4-65, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

On the basis of the data submitted to the agency, FDA concludes that a

one-time temporary storage of Source Plasma (Human) at a temperature between −20° and −5° C for a period up to 72 hours will not affect the safety, purity, potency, or effectiveness of derivatives prepared from the plasma. Therefore, the PMA recommendation to amend the storage temperature regulations is accepted to the extent set forth in this document. No data have been submitted, however, to support the potency levels of clotting factor derivatives prepared from Source Plasma (Human) exposed to more than one episode of temperature elevation. Therefore, this proposal would amend § 640.76 by designating existing paragraph (a) as (a)(1) and by adding a new paragraph (a)(2) to permit only one inadvertent episode (i.e., an unforeseen occurrence in spite of compliance with good manufacturing practices) of temperature elevation without requiring relabeling of the units as "Source Plasma (Human) Salvaged." The proposed amendment would also require that appropriate records be maintained and copies provided to the plasma derivatives manufacturer, specifying the units involved, that there was no more than one episode of temperature elevation, that the temperature did not rise to warmer than −5° C, and that the period of exposure was no more than 72 hours. In addition, the proposed amendment would define the term, "inadvertently exposed", in paragraphs (a)(1), (2), and (b) by specifying its relationship to the good manufacturing practices standard. Paragraph headings are also proposed for paragraphs (a), (b), and (c).

The Food and Drug Administration has carefully considered the environmental effects of the proposed regulation and, because the proposed action will not significantly affect the quality of the human environment, has concluded that an environmental impact statement is not required. A copy of the environmental impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Therefore, under the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)) and under authority delegated to him (21 CFR 5.1), the Commissioner of Food and Drugs proposes to amend Part 640 by revising § 640.76 to read as follows:

* * * * *

§ 640.76

* * * * *

[FR Doc. 79-32218 Filed 10-18-79; 8:45 am]

50.—Immune Serum Globulin

† 50.3 Notice of Availability of Guidelines—April 14, 1978

- 43 FR 15779 -

[Docket No. 78D-0075]

IMMUNE SERUM GLOBULIN (HUMAN)

Availability of Guidelines

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: This document announces the availability of guidelines for the package insert for Immune Serum Globulin (Human). The guidelines are intended to promote prompt review and evaluation of labeling submitted with new and amended license applications by creating a uniform format and content.

DATE: Written comments by May 15, 1978.

ADDRESS: Requests for a copy of the guidelines and submission of written comments may be addressed to the Hearing Clerk (HFC-20), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Michael L. Hooton, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20014, 301-443-1306.

SUPPLEMENTARY INFORMATION: The Food and Drug Administration notice that a copy of guidelines for the package insert for Immune Serum Globulin (Human) is on display in the office of the Hearing Clerk, Food and Drug Administration at the above address between the hours of 9 a.m. and

4 p.m., Monday through Friday. Immune Serum Globulin (Human) is a licensed product defined as a sterile solution containing antibodies derived from human blood (21 CFR 640.100). Its major use is for the treatment of hepatitis A, an acute infectious, inflammatory disease of the liver caused by hepatitis A virus.

The guidelines are intended to produce consistency in the format and content of package inserts for Immune Serum Globulin (Human) produced by licensed manufacturers, thereby promot'ng prompt review and evaluation of the labeling described in new and amended license applications. The guidelines also include information concerning current medical knowledge and practice. Copies of the guidelines are being furnished to licensed manufacturers of Immune Serum Globulin (Human). Other persons interested in obtaining copies of the guidelines may contact the office of the Hearing Clerk, Food and Drug Administration at the above address.

Interested persons may, on or before May 15, 1978 submit written comments (preferably four copies, identified with the Hearing Clerk docket number found in brackets in the heading of this document) to the Hearing Clerk (HFC-20), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

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[FR Doc. 78-9923 Filed 4-13-78; 8:45 am]

XI. Diagnostic Substances

	Page
B. Dermal Tests	445
†25.—Adsorbed Diptheria and Tetanus Toxoids	616
†25.1 Notice of Availability of Guideline—April 13, 1979 (44 FR 22178)	616

B. Dermal Tests

†25.—Adsorbed Diphtheria and Tetanus Toxoids

†25.1 Notice of Availability of Guideline—April 13, 1979

[Docket No. 78D-0438]

Adsorbed Diphtheria and Tetanus Toxoids; Availability of Guideline

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The agency announces the availability of a guideline for interpretation of potency test results for all forms of adsorbed diphtheria and tetanus toxoids.

ADDRESS: Written comments may be submitted to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Iris Hyman, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20014, 301-443-1306.

SUPPLEMENTARY INFORMATION: The guideline prepared by the Bureau of Biologics covers potency tests performed on all forms of adsorbed diphtheria and tetanus toxoids, including Diphtheria Toxoid Adsorbed, Tetanus Toxoid Adsorbed, Diphtheria and Tetanus Toxoid Adsorbed, Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), and Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed. Adsorbed toxoids are the insoluble, precipitated form of the soluble, parent toxoid. Both forms are used in the prevention of the diseases diphtheria and tetanus.

Currently, the only guidelines controlling these products are minimum requirements, each of which gives slightly different wording for the potency tests performed on all forms of the adsorbed toxoids. This has led to confusion and to a variety of interpretations by manufacturers. The new guideline is intended to clarify the definition of a valid potency test endpoint to ensure standardization of performance and reporting of potency test results on protocols for release. Because of the brevity of the guideline, it is reproduced in this notice, as follows:

GUIDELINE FOR INTERPRETATION OF POTENCY TEST RESULTS FOR ALL FORMS OF ADSORBED DIPHTHERIA AND TETANUS TOXOIDS

For a valid potency test, each control animal must die in less than 96 hours. For the lot to pass, each test animal must survive for more than 96 hours at the minimum unit level required.

Copies of the guideline are being furnished to all licensed manufacturers of adsorbed tetanus and diphtheria toxoids. Other persons interested in obtaining copies of the minimum requirements, as amended, and guideline may contact the office of the Hearing Clerk, Food and Drug Administration, at the above address.

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[FR Doc. 79-11451 Filed 4-12-79; 8:45 am]

XII. Other Products

	Page
B. Allergenic Products	450
5.—Skin Test Antigen Efficacy Review	450
†5.2 Final Regulation—July 10, 1979 (44 FR 40284)	617
†12.—Source Material for Allergenic Products	625
†12.1 Proposal—September 26, 1978 (43 FR 43472)	625
†12.2 Extension of Time for Comments—January 23, 1979 (44 FR 4707)	627
†14.—Allergenic Product Multiple Dose Containers	628
†14.1 Proposal—July 14, 1978 (43 FR 30302)	628
†16.—Antigen E Potency Test	629
†16.1 Proposal—August 3, 1979 (44 FR 45642)	629
†16.2 Extension of Time for Comments—October 19, 1979 (44 FR 60333)	632

B. Allergenic Products

5.—Skin Test Antigen Efficacy Review

†5.2 Final Regulation—July 10, 1979

- 44 FR 40284 -

[Docket No. 76N-0480]

Skin Test Antigens; Implementation of Efficacy Review

AGENCY: Food and Drug Administration.

ACTION: Final Rule.

SUMMARY: The Food and Drug Administration (FDA) is amending certain licensing and standards provisions of the biologics regulations in response to the recommendations of the Panel on Review of Skin Test Antigens. The agency is announcing its adoption of the Panel Report, with modifications of certain portions, based on comments received. The modifications are made for clarity and regulatory accuracy and to reflect any new information that has come to the agency's attention. In addition, the agency is reclassifying Histoplasmin, manufactured by Parke, Davis & Co. and Tuberculin, PPD, Multiple Puncture Device (Heaf) manufactured by Connaught Laboratories Limited from Category IIIA to Category I.

DATES: Effective July 10, 1979, except that recommended labeling changes become effective January 7, 1980.

ADDRESS: Additional background data and information are on public display in the office of the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Michael L. Hooton, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20205, 301-443-1306.

SUPPLEMENTARY INFORMATION: In the FEDERAL REGISTER of September 30, 1977

- 40285 -

(42 FR 52674), FDA published a proposal containing findings of the Panel on Review of Skin Test Antigens. The Panel evaluated the safety and effectiveness of 23 skin test antigen products and recommended that: (a) 5 products be placed in Category I (those biological products determined to be safe, effective, and not misbranded); (b) 2 products be placed in Category II (those biological products determined to be unsafe, ineffective, or mis-

branded); (c) 6 products be placed in Category IIIA (those biological products for which available data are insufficient to classify their safety and effectiveness but which may remain in the interstate commerce pending completion of testing and conformance with the recommendations of the Panel); and (d) 10 products be placed in Category IIIB (those biological products for which available data are insufficient to classify their safety and effectiveness and which should not continue in interstate commerce).

The Commissioner of Food and Drugs agreed with the Panel's recommendations concerning the classification of these products and accordingly announced the intention to publish a Notice of Opportunity for Hearing to revoke the licenses for those products placed in Categories II and IIIB. At the request of the licensees, the licenses for the 2 products in Category II and 2 of the 10 products in Category IIIB were revoked before publication of the Notice of Opportunity for Hearing. The Notice of Opportunity for Hearing for the remaining 8 Category IIIB products was published in the FEDERAL REGISTER of October 28, 1977 (42 FR 56800). Interested persons were advised that they could submit additional data in response to the revocation notices; for products placed in Category IIIA, comments or additional data concerning the classification were also invited. Because manufacturers of those licensed products placed in Category IIIB either did not request a hearing, requested a hearing and submitted additional data that justified reclassification of products without the need for the requested hearing, or requested that the licenses be revoked, FDA published in the FEDERAL REGISTER of October 27, 1978 (43 FR 50250), a notice reclassifying certain products into Category IIIA and revoking the remaining product licenses.

In addition, the September 1977 proposal contained the Commissioner's responses to other Panel recommendations concerning the testing, content, and labeling of skin test antigens. In view of these recommendations, the Commissioner proposed the following amendments to the biologics regulations:

(1) In § 601.25(h) (21 CFR 601.25(h)), to require that the labeling for Category IIIA skin test antigens contain a prominent boxed statement referencing the Panel's findings of insufficient data on safety and effectiveness, and that written informed consent be obtained from participants in the additional studies performed pursuant to § 601.25(h);

(2) In § 610.13 (21 CFR 610.13), to clarify the regulation by specifying that products need to be free of avoidable extraneous material;

(3) In § 650.13 (21 CFR 650.13), to require chemical characterization of each batch of powdered tuberculin material; and

(4) To redesignate existing § 650.15 as § 650.16 *Equivalent methods* and add new § 650.15 to require potency testing of each batch of tuberculin material in humans.

Interested persons were given until November 29, 1977 to file comments on these proposals with the Hearing Clerk. Eleven letters were received, many of which contained more than one comment. This final rule announces the agency's adoption of the Panel's conclusions and recommendations for classifying skin test antigens, as modified on the basis of comments received and FDA's independent evaluation of the Panel Report. Modifications have been made for clarity and regulatory accuracy, and to reflect any new information that has come to the agency's attention. FDA's agreement with comments suggesting modification of the Panel's findings is reflected in the following summary of the comments and FDA's responses to them.

Panel Report

Basis of Evaluation

1. One comment concerning the Panel's statement on the characteristics of an ideal skin test antigen (42 FR 52675-6) suggested that the skin test material should not cause a local (irritant) reaction, i.e., it should be used at the concentration that produces an antigenic response only.

FDA agrees and interprets the Panel's use of the phrase "immune response" to mean that the skin test antigen should be used at a concentra-

tion that induces a specific skin reaction only and not a local irritant reaction.

2. One comment concerning test material (paragraph (2) *Test material,* 42 FR 52675) suggested that diluents should be used as control materials and should be injected separately and simultaneously when the skin test antigen is injected.

The Panel recommended that the solution (diluents) into which the testing material is dissolved must neither sensitize the immune system nor elicit any other form of host reaction, local or systemic. As a requisite for approval of a license application for skin test antigens, a product must be tested in nonsensitive individuals, thereby detecting any reactions that may be attributed to the diluent used. Therefore, it is unnecessary to subject a person to an additional and unwarranted injection of control diluent. Accordingly, FDA rejects the comment.

3. One comment concerning the test method (paragraph (3) *Test method,* 42 FR 52675) stated that it is difficult precisely to inject skin test antigens with resulting clear-cut reproducible reactions in the host as prescribed for an ideal skin test method. The comment suggested that it would be more realistic to provide a range of reaction sizes (in millimeters) for each concentration of antigen.

The Panel noted in its report that the ideal skin test method is a conceptualization that the scientific community should strive to achieve. The agency agrees with the comment that given the current state of the art, it is not possible to require all the characteristics of the ideal skin test method. New and modified methods will be required as they are developed and are proven to be more sensitive and accurate.

Histoplasmin by Parke, Davis & Co.

4. The Panel recommended in its report that Histoplasmin manufactured by Parke, Davis and Company be placed in Category IIIA because the available data were insufficient to satisfy its safety and effectiveness. Since publication of the Panel's report, the firm has submitted data with an amended license application demonstrating safety and effectiveness of its product. FDA has reviewed the data and found them adequate to approve the license amendment and reclassify the product to Category I. Accordingly, Histoplasmin manufactured by Parke, Davis and Company is reclassified from Category IIIA to Category I.

Mumps Skin Test Antigen

5. One comment requested that Mumps Skin Test Antigen manufactured by Eli Lilly & Co. be placed in Category IIIA rather than IIIB for its use in assessing immunocompetence.

FDA advises that Mumps Skin Test Antigen manufactured by Eli Lilly & Co. was assigned to Category IIIB by the Panel for its licensed and labeled use for identifying immunity to mumps virus infection. However, the Panel noted the widespread use and apparent value of the product for the purpose of ascertaining immunocompetence and recommended that additional data be submitted to demonstrate the product's safety and effectiveness for this use. Eli Lilly & Co. has submitted data in support of using the product for testing immunocompetence. As stated in the October 1978 notice, the Commissioner decided to hold in abeyance a ruling on Eli Lilly & Co.'s request for a hearing, pending receipt from the firm and evaluation by FDA of an appropriate license amendment and a commitment to undertake additional studies as required by § 601.25(h)(1) (21 CFR 601.25(h)(1)). The amendment has been submitted and Mumps Skin Test Antigen has been placed into Category IIIA for further evaluation of its use for immunocompetence testing. Therefore, no hearing will be necessary.

Tuberculin, Old, General Statement; Characteristics of Effectiveness

6. One comment concerning the measurement in the test method for Tuberculin, Old suggested that a statement be added to distinguish the type of reaction produced by Tuberculin Mono-Vacc and other multiple puncture devices.

Although the comment does not require a change in the regulation, the

agency agrees that it would be appropriate to distinguish the type of reaction described in the comment. Thus, the Panel Report is adopted with a modification in paragraph (ii)(2) *Measurement* (42 FR 52700) to delete the last sentence and add a new sentence as follows:

The close spacing of the Mono-Vacc points usually produces a single area of induration while the more distant spacing of other multiple puncture devices may produce multiple areas of induration which may coalesce to form a circular reaction.

Tuberculin, Old (Tine Test) by Lederle; Characteristics of Effectiveness

7. The agency advises that in the FEDERAL REGISTER of July 29, 1977 (42 FR 38567), FDA amended § 650.14 (21 CFR 650.14) to change the assay requirements for multiple puncture devices from ±50 percent of the tuberculin units claimed by the manufacturer in its license application to ±20 percent of the tuberculin units.

The Panel Report to the agency did not reflect the amendment to § 650.14 published in the FEDERAL REGISTER of July 29, 1977. Therefore, to reflect the correct assay requirement accurately, the Panel Report is adopted with a modification in paragraph (i)(3) *Standardization* in the discussion concerning test material for Tuberculin, Old (Tine Test) by Lederle, (42 FR 52702), to revise the phrase "the average potency for each Tine Test unit must be equivalent to $\frac{1}{2700}$ to $\frac{1}{1330}$ of the undiluted U.S. Standard Old Tuberculin (an allowable variation of 33 percent)" to read "the average potency of each Tine Test unit must be equivalent to $\frac{1}{1666}$ to $\frac{1}{2500}$ of the undiluted U.S. Standard Old Tuberculin (an allowable variation of 20 percent)."

8. One comment concerning certain Panel recommendations on Lederle's Tuberculin, Old (Tine Test), (paragraph 4, *Recommendations* (b), 42 FR 52703) stated that use of individuals with bacteriologically confirmed tuberculosis in in vivo testing with tuberculin may create a legal dilemma for manufacturers because tuberculin testing of infective persons may reactivate quiescent or healed-over lesions. No data accompanied the comment.

The agency is not aware of any information to support the suggestion that tuberculin testing of infected persons may reactivate quiescent foci. Skin testing of individuals, both infected and noninfected, has been carried out for many years in millions of persons and when the correct doses are properly administered, adverse reactions to tuberculin are limited only to those who are very sensitive. These reactions are localized and usually self limited. Accordingly, the comment is rejected.

Tuberculin, Old by Institut Merieux; Characteristics of Effectiveness

9. One comment on test material standardization for Institut Merieux's Tuberculin, Old recommended that, to ensure reproducibility, the degree of reactivity should be tested with material derived from 20 randomly selected Mono-Vacc test devices as required for the Lederle Laboratories Division product (characteristics of effectiveness, (i)(3) *Standardization*) at 42 FR 52702.

Although the comment does not require a change in the regulation, the agency agrees that it would be appropriate to clarify the procedure for standardization of Institut Merieux's Tuberculin, Old test material. Thus, the Panel Report is adopted with a modification in characteristics of effectiveness, (i)(3) *Standardization*, (42 FR 52708) to revise the first paragraph to read as follows:

The standardization of each lot is accomplished by injecting 0.5, 1, 2, and 4 TU of the U.S. Standard tuberculin (Bureau of Biologics) intracutaneously by the Mantoux method into hypersensitive guinea pigs and comparing the degree of reactivity to four comparative levels of activity of the test lot with material derived from 20 randomly selected Mono-Vacc test devices.

Tuberculin, PPD, Multiple Puncture Device (Aplitest) by Parke-Davis

10. One comment concerning the Panel's quality control recommendations for Parke-Davis' Tuberculin, PPD, Multiple Puncture Device (Aplitest) (paragraph 4. *Recommendations* (a), 42 FR 52715) suggested that the required quality control test is unnecessary because, except for human error, the mechanical dipping process will always coat tines.

FDA believes that the required testing is necessary to compensate for human error and to ensure that all tines are dipped satisfactorily, thus preventing the marketing of inadequately coated tines that would result in false negative reactions. Accordingly, the comment is rejected.

Tuberculin, PPD (Mantoux) by Connaught

11. One comment concerning Connaught's Tuberculin, PPD (Mantoux) suggested that the title should include the trade name, "Tubersol®," after the word "Mantoux."

The agency advises that the trade name "Tubersol®" for Connaught's Tuberculin, PPD (Mantoux) was inadvertently omitted from the September 30, 1977 proposal. Wherever the name "Tuberculin, PPD (Mantoux)" by Connaught appears in the proposal, it should be considered to include the trade name "Tubersol®." For consistency, the agency also advises that the name of the Parke, Davis & Co. Tuberculin, PPD product should read "Tuberculin, PPD (Mantoux) Aplisol®" wherever it appears.

12. Connaught Laboratories Limited commented that certain portions of the Panel Report under the heading "Characteristics of Effectiveness" should be clarified to reflect accurately the characteristics of Tuberculin, PPD (Mantoux) Tubersol®. Although the comment does not require a change in the regulation, the agency agrees that it would be appropriate to clarify the Panel Report. Therefore, the Panel

– 40287 –

Report is adopted with the following modifications:

(a) Paragraph (i)(1) *Chemical composition* (42 FR 52716) is modified by revising the last sentence to read as follows:

The Kjeldahl nitrogen content is used in the preparation of a 1 mg/ml stock solution from the Master Batch PPD-CT68. One mg PPD-CT68 has been found by the Kjeldahl method to correspond to 0.91 plus or minus 0.02 mg of proteins.

(b) In (i)(3) *Standardization* (42 FR 52716), the last paragraph is modified to read as follows:

Bioequivalency of PPD-CT68 to PPD-S was determined in man, and the 5 TU bioequivalent PPD-CT68 preparation is confirmed on the basis of the guinea pig potency test. The 1 TU and 250 TU strengths are made by appropriate dilutions of the stock material in reference to the 5 TU dose. They are therefore calculated potencies and not directly bioequivalent to a standard, although each strength is standardized in guinea pigs against PPD-S and the Connaught Laboratories Limited house standard Tuberculin, PPD. This would seem to be an acceptable compromise, however, since most of the clinical data on which interpretation of reaction sizes are based have been collected only with the 5 TU dose. One TU and 250 TU PPD are used only in special instances and interpretations of reactions with these doses are limited.

(c) The typographical error in paragraph (i)(4) *Stability* (42 FR 52716) is corrected by revising the phrase "50 PPm" to read "50 ppm."

(d) In 4. *Recommendations* the first sentence of paragraph (b) (42 FR 52717) is modified to read as follows:

The labeling should indicate that storage in secondary containers (such as a syringe) is not recommended because of possible contamination of the product during transfer from container to container.

Tuberculin, PPD, Multiple Puncture Device (Heaf) by Connaught

13. Connaught Laboratories Limited also commented that certain portions of the Panel Report under discussion of "Tuberculin, PPD, Multiple Puncture Device (Heaf)" should be clarified to describe this product accurately. Although the comment does not require a change in the regulation, the agency agrees that it would be appropriate to clarify the Panel Report. Thus, the Panel Report is adopted with the following modifications:

(a) The typographical error "250 TP" in paragraph 3. (a) *Effectiveness* (42 FR 52717), in the next to the last sentence is corrected to read "250 TU."

(b) The third sentence of paragraph 3. (a)(i)(3) *Standardization* (42 FR 52717) is modified to read as follows:

The reaction sites are randomized and the reactions are read blindly.

(c) Paragraph 3. (a)(i)(1)(7) *Diluent* (42 FR 52717) is modified to read as follows:

The material itself is prepared in a solution which contains sodium phosphate sodium chloride, 50 percent w/v glycerol, and 0.5 percent w/v phenol, and is not known to be sensitizing. No further diluent is used.

14. Connaught Laboratories Limited also requested reclassification of its Tuberculin, PPD, Multiple Puncture Device (Heaf) from Category IIIA to Category I and submitted data from clinical studies performed on 50 individuals with bacteriologically confirmed tuberculosis.

FDA finds that the data submitted adequately support reclassification of the Tuberculin, PPD, Multiple Puncture Device from Category IIIA to Category I. Accordingly, the product is reclassified to Category I.

Proposed Amendments to the Regulations

15. One comment concerning proposed § 601.25(h)(4) objected to the requirement that labeling and promotional material for products requiring additional studies contain a box statement concerning the effectiveness of the product because the statement will result in a marked reduction in the use of the product by the medical community.

FDA does not agree. Section 601.25(h)(4), requiring the boxed labeling referred to in the comment, was codified in the final rule concerning Bacterial Vaccines and Bacterial Antigens with "No U.S. Standards of Potency," which was published in the FEDERAL REGISTER of January 5, 1979 (44 FR 1544). The reponse to comment 8 of that final rule (see 44 FR 1547) sets forth the reasons for the adoption of the boxed labeling, which references the need for further data to establish effectiveness of Category IIIA products fully.

Section 601.25(h)(5), requiring written informed consent from participants in the requisite additional studies on Category IIIA products, was also codified in the January 5, 1979 final rule concerning Bacterial Vaccines and Bacterial Antigens with "No U.S. Standards of Potency." No comments were received on the proposal to require informed consent for studies on skin test antigens. The agency has now concluded that § 601.25 should be amended as proposed for skin test antigens (1) in paragraph (h)(4) to preclude misleading labeling, which results in misbranding of the products, by requiring disclosure in the boxed labeling that the data in support of the products' safety and effectiveness are currently insufficient, and (2) in paragraph (h)(5) to give participants in the additional studies an explanation of the product and purpose of the study, and provide them a clear opportunity to refuse to participate in the study. Accordingly, the comment is rejected and § 601.25(h) (4) and (5) is amended by requiring skin test antigens to meet the labeling provisions set forth in each paragraph.

16. One comment concerning §§ 650.13 and 650.15 recommended use of the term "master lot" rather than "batch" in the regulations.

FDA believes that the term "batch" is more appropriate. "Master lot" may be confused with the term "lot," which is used in the biologics field to identify final production material. In addition, use of the term "batch" for tuberculin products is consistent with its use for other drug products (see § 210.3(b)(2) (21 CFR 210.3(b)(2))). Each batch of tuberculin material is intended to last for a number of years and is chemically characterized and tested for potency in humans. Tuberculin production lots are final material manufactured from a batch of material. Accordingly, the comment is rejected and the term "batch" is retained in §§ 650.13(c) and 650.15 (a) and (b).

17. Four comments on the Panel's recommendations for tuberculin products and proposed § 650.15(a) expressed concern over the requirement that multiple puncture devices for screening purposes be sufficiently sensitive to elicit reactions in 100 percent of at least 50 persons who are known to have had bacteriologically confirmed tuberculosis. The comments suggested that a margin be permitted for human error and that there is no practical difference in the effectiveness of tuberculin materials that elicit positive reactions in 95 percent of persons tested.

FDA acknowledges, and experience has demonstrated, that certain false positive and false negative reactions are associated with all tuberculin tests.

Consequently, the 100 percent reactivity requirement may result in rejection of a satisfactory batch of tuberculin material. Accordingly, the comment is accepted and § 650.15(a) is amended to require that the sensitivity of each batch of tuberculin material be demonstrated to

be sufficient to elicit positive reactions at a 95 percent rate.

18. One comment concerning proposed § 650.15(a) requested a definition of what constitutes a positive skin test reaction for multiple puncture devices. Another comment recommended that a positive test for certain multiple puncture devices be defined as an induration of 2 millimeters (mm) or more at one or more of the puncture sites and a positive Mantoux test be defined as an induration of 5 mm or more.

FDA agrees that the reaction sizes recommended in the comment will ensure that the batch being tested is at least as sensitive as the standard and will define the testing requirements for batches of both liquid tuberculins and tuberculins dried on tines in § 650.15(a). Accordingly, the comment is accepted and § 650.15(a) is amended to require minimum reaction sizes of 2 mm or more at one or more of the puncture sites or at a coalescence of more than one site for all multiple puncture devices and 5 mm or more for the Mantoux test.

19. One comment concerning proposed § 650.15(a) recommended that the proposed standards include defined retest provisions, as has been permitted under § 650.14 concerning animal potency testing.

FDA advises that § 650.15(a) permits additional data to be accumulated to obtain the 95 percent reactivity rate in bacteriologically confirmed tuberculosis subjects by testing additional individuals who react to the 5 TU dose in the Mantoux test. To clarify the retest provisions concerning animal potency tests, the agency is amending § 650.14 by revising the title of the section and by adding the phrase "using results from all valid tests performed" to the last sentence in paragraph (b).

20. One comment on proposed § 650.15(a) questioned the availability of PPD–S for use in characterizing master lots of tuberculin.

FDA advises that the Bureau of Biologics will supply adequate amounts of PPD–S reference material to all manufacturers for use in characterizing tuberculin products.

21. One comment on proposed § 650.15(b) suggested that the requirement for potency testing in the population subgroups specified under paragraph (b)(2) may not be achievable because of the problem of finding such individuals in certain locations in the United States.

FDA believes that manufacturers will be able to locate the population subgroups specified under § 650.15(b). Moreover, the testing is required only for a batch. A batch may be manufactured from large volumes of pooled material and should last for a number of years. Accordingly, the burden imposed by the testing requirement will not be frequent or continuous. For these reasons, the comment is rejected.

22. One comment suggested that proposed § 650.15(b) be modified to require that the effectiveness of each batch of tuberculin material for use by the Mantoux method include a determination of the bioequivalent dose by comparing the product with a standard using dose response curves for two population subgroups known or presumed to be infected with *Mycobacterium tuberculosis* and a third population subgroup composed of persons presumed to be infected with other mycobacteria. The comment suggested that the bioequivalent dose then be verified by comparing the distribution of reaction sizes of the product and standard separately for each of those three population subgroups and a fourth subgroup composed of persons presumed to be without mycobacterial infection.

FDA believes that the use of four separate population subgroups for testing each batch of tuberculin is not warranted. Tuberculin products are primarily intended to diagnose people infected with *Mycobacterium tuberculosis*, and it is necessary only that the selective dose be bioequivalent to the 5

TU of the standard as determined by the dose response assays identified in § 650.15(b). Accordingly, the comment is rejected.

23. One comment on proposed § 650.15 suggested that persons performing the tests will anticipate that their subjects should be positive. Because of this bias, borderline negative reactions for both tests may be read as positive. The comment also suggested that bias would not necessarily be predictive for both the testing material and the control in the same subject because the two tests may be read by different persons and because bias may play a part in one test and not in the other.

FDA agrees that bias may enter into the evaluation of the test results. To preclude such bias, the agency is amending § 650.15 by adding a new paragraph (c) requiring that all trials be performed in randomized double-blind fashion whenever possible and all reactions in each test subject be read by more than one competent and responsible individual.

24. One comment on proposed § 650.15 suggested that the Bureau of Biologics conduct and monitor the human testing that is required of manufacturers in the proposed regulations. The comment provided no reason for the suggestion.

The agency advises that it is the manufacturer's responsibility to conduct testing to develop data supporting the safety, effectiveness, and quality of a drug product. FDA will review the resulting data to determine whether the product is satisfactory for release. Accordingly, the comment is rejected.

Having considered the comments and other relevant information, FDA concludes that the proposal, with changes, is adopted as set forth below.

(a) *Category I. Biological products determined to be safe and effective and not misbranded and which should continue in interstate commerce.* Histoplasma, Parke, Davis & Co., License No. 1; Tuberculin, Old (Multiple Puncture Device), Lederle Laboratories Division, American Cyanamid Co., License No. 17; Tuberculin, Old (Multiple Puncture Device), Institut Merieux, License No. 384; Tuberculin, PPD (Mantoux) Tubersol ®, Connaught Laboratories Limited, License No. 73; Tuberculin, PPD (Mantoux) Aplisol ®, Parke, Davis & Co., License No. 1; Tuberculin, PPD, Multiple Puncture Device, (Aplitest), Parke, Davis & Co., License No. 1; and Tuberculin, PPD, Multiple Puncture Device (Heaf), Connaught Laboratories Limited, License No. 73. Licenses remain in effect for these products pending conformance with the Panel's recommendations. Labeling changes recommended by the Panel and now adopted by FDA become effective January 7, 1980.

(b) *Category II. Biological products determined to be unsafe or ineffective or to be misbranded and which should not continue in interstate commerce.* At the request of the manufacturer, Category II product licenses were revoked before publication of the Panel Report, as announced in the FEDERAL REGISTER proposal on September 30, 1977 (42 FR 52721).

(c) *Category IIIA. Biological products for which available data are insufficient to classify their safety and effectiveness but which may remain in interstate commerce.* Coccidioidin, Cutter Laboratories, Inc., License No. 8; Coccidioidin, Iatric Corporation, License No. 416; Histoplasmin, Bureau of Laboratories, Michigan Department of Public Health, License No. 99; Diphtheria Toxin for Schick Test, Massachusetts Public Health Biologic Laboratories, License No. 64; and Mumps Skin Test Antigen, Eli Lilly & Co., License No. 56. Licenses remain in

– 40289 –

effect for these Category IIIA products pending conformance with the Panel's recommendations and completion of testing in accordance with § 601.25(h) (21 CFR 601.25(h)).

For products now herein classified in Category IIIA for which license revocations have not been issued at the request of the licensee, manufacturers shall submit, on or before August 9, 1979, a written statement of the studies that the licensee proposes to undertake to resolve the questions raised about the products. If no such commitment is made or adequate or appropriate studies are not undertaken, the Commissioner shall institute proceed-

ings to revoke the license (21 CFR 601.25(h)(1)). Licenses for Category IIIA products will remain in effect pending the conduct of studies as recommended by the Panel and adopted by the Commissioner.

Labeling changes recommended by the Panel and now adopted by FDA become effective January 7, 1980.

(d) *Category IIIB. Biological products for which available data are insufficient to classify their safety and effectiveness and which should not continue in interstate commerce.* Product licenses for Category IIIB products were revoked or the products were reclassified to Category IIIA as announced in the FEDERAL REGISTER notice of revocations and reclassifications on October 27, 1978 (43 FR 50250).

A summary of the category changes that have been made from those originally recommended by the Panel is as follows:

(1) Data submitted by Eli Lilly & Co. have been found adequate to reclassify its Mumps Skin Test Antigen from Category IIIB to Category IIIA;

(2) Data submitted by Connaught Laboratories Limited have been found adequate to reclassify its Tuberculin, PPD Multiple Puncture Device (Heaf) from Category IIIA to Category I; and

(3) Data submitted by Parke, Davis & Co. with an amended license application for a dye-free, stable product have been found adequate to approve the license amendment and to reclassify the firm's Histoplasmin from Category IIIA to Category I.

In addition, FDA had reclassified Diphtheria Toxin for Schick Test and Schick Test Control, manufactured by Texas Department of Health Resources, from Category IIIB to Category IIIA. However, the establishment and product licenses of this manufacturer were later revoked at the manufacturer's request.

Additional background data and information on which the agency relies in promulgating these regulations are on public display in the office of the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040-1042 as amended, 1050-1053 as amended, 1055-1056 as amended (21 U.S.C. 321, 352, 355, 371)), the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)), and the Administrative Procedure Act (secs. 4, 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 702, 703, 704)), and under authority delegated to the Commissioner (21 CFR 5.1), Parts 601, 610, and 650 are amended as follows:

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§ 601.25

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§ 610.13

Part 650

§ 650.13
§ 650.14
§ 650.15
§ 650.16

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[FR Doc. 79-21201 Filed 7-9-79; 8:45 am]

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† 12.—Source Material for Allergenic Products

† 12.1 Proposal—September 26, 1978

– 43 FR 43472 –

[21 CFR Part 680]

[Docket No. 78N-0235]

ALLERGENIC PRODUCTS

Proposed Criteria for Source Material

AGENCY: Food and Drug Administration.

ACTION: Proposed Rule.

SUMMARY: The Commissioner of Food and Drugs is proposing to amend the biologics regulations concerning Allergenic Products. These amendments would establish additional criteria for source material to ensure the safety, purity, potency, and effectiveness of the final Allergenic Product.

DATE: Comments by November 26, 1978.

ADDRESS: Written comments to the Hearing Clerk (HFA-305), Rm. 4-65,

Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Michael L. Hooton, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20014, 301-443-1306.

SUPPLEMENTARY INFORMATION: Licensed Allergenic Products are widely used by physicians for the diagnosis and treatment of reactions (allergies) thought to be caused by or associated with allergenic substances (allergens). Source (starting) material used to produce Allergenic Products includes allergens such as molds, feathers, and hairs. It is essential that the source material be suitable for manufacture into final Allergenic Products, most of which are administered by injection.

The use of an Allergenic Product produced from molds that have been contaminated or inadequately identified may result in false positive reactions in the patient or may cause sensitization of the patient to the mold. Accordingly, proposed § 680.1(b)(2)(i) would require that molds used as a source material (1) meet the requirements concerning storage, maintenance, identity, and verification prescribed in § 610.18 (21 CFR 610.18) and (2) conform to the quality and purity requirements prescribed in § 680.2 (a) and (b) (21 CFR 680.2 (a) and (b)). Proposed § 680.1(b)(2)(ii) would require that molds contain no foreign materials.

Allergenic Products produced from animal origin may also be unsuitable for injection into humans if the source material (feathers, hair, and danders) is prepared from sick animals or animals that have died from undetermined causes. Accordingly, the proposed regulations would require (1) in §680.1(b)(3)(i) that pets, farm animals, and other domesticated mammals and birds meet the requirements concerning care, quarantine, immunization against tetanus, and reporting of certain diseases that are prescribed in § 600.11(f)(1),(2),(3), and (6) (21 CFR 600.11(f)(1),(2),(3), and (6)) and that animals be in good health at the end of the quarantine period as determined by a licensed veterinarian; (2) in § 680.1(b)(3)(ii) that wild mammals and birds that cannot meet the requirements prescribed in § 600.11(f) may be used as a source of material only when the package label and the package insert of the final Allergenic Product state that it was prepared from animals whose state of health could not be determined; and (3) in § 680.1(b)(3)(iii) that dead animals may be used as source material only if the animals are properly stored so that the allergen will not be adversely affected and if the other applicable requirements concerning animals in § 680.1(b)(3) are met. The proposed regulations also would provide, in § 680.1(b)(3)(iv), that mammals and birds that have been inspected by the U.S. Department of Agriculture and found suitable as food are exempt from the requirements of proposed § 680.1(b)(3)(i) and (ii).

Many licensed Allergenic Products are manufactured from source material that is propagated and prepared at nonlicensed establishments. The licensed final product manufacturer has no assurance that the source material has been properly identified, obtained, or processed. Therefore, the Commissioner is proposing to add a new § 680.1(c) to require that manufacturers of the licensed final product establish and maintain a written agreement with each nonlicensed source material supplier that will permit authorized representatives of the Food and Drug Administration (FDA) to inspect the nonlicensed establishment during reasonable business hours. The Commissioner recognizes that a written agreement and inspection may normally be unnecessary and impractical when the source material is to be obtained under certain circumstances (e.g., house dust from an individual's home) in which inspection will provide no additional assurances of safety. Accordingly, proposed § 680.1(c)(2) would provide exemptions to the agreement and inspection requirements.

The biologics regulations currently require, in § 600.12 (21 CFR 600.12), that records be made concurrently with the performance of each step in the manufacture and distribution of

products. Proposed § 680.2(f) would require that a copy of such records be available at the establishment of the licensed manufacturer of the finished product. This record requirement will facilitate a complete and expeditious FDA inspection of the licensed manufacturer of the finished product.

Although numerous substances (e.g., molds, feathers, hair, dander, saliva, insects, venoms, dust, poison ivy, and pollens) are used as source material for manufacture into licensed Allergenic Products, the proposed requirements concerning suitability of source materials in § 680.1(b) (2) and (3) would cover only molds and certain

- 43473 -

animals used as allergenic source materials. In the future, as technical knowledge permits, the biologics regulations will be amended to include regulations to govern the propagation or preparation of other specific allergenic sources, such as invertebrate animals, pollens, and foods. The proposed requirements concerning FDA inspection of nonlicensed establishments and recordkeeping in §§ 680.1(c) and 680.2(f) would apply to all licensed allergenic products manufacturers who use any allergenic source material to manufacture a final product.

The Commissioner has carefully considered the environmental effects of the proposed regulation and, because the proposed action will not significantly affect the quality of the human environment, has concluded that an environmental impact statement is not required. A copy of the environmental impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Therefore, under the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)) and under authority delegated to him (21 CFR 5.1), the Commissioner proposes to amend Part 680 of Subchapter F of Title 21 of the Code of Federal Regulations as follows:

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Part 680

§ 680.1

§ 680.2

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[FR Doc. 78-26949 Filed 9-25-78; 8:45 am]

† 12.2 Extension of Time for Comments—January 23, 1979

- 44 FR 4707 -

[21 CFR Part 680]

[Docket No. 78N-0235]

CRITERIA FOR SOURCE MATERIAL OF ALLERGENIC PRODUCTS

Extension of Comment Period and Notice of Public Meeting

AGENCY: Food and Drug Administration.

ACTION: Extension of Comment Period on Proposed Rule.

SUMMARY: This document extends the period for submitting comments on proposed additional criteria for source material of Allergenic Products and announces that a public meeting will be held to give interested persons an opportunity to participate in a discussion of the proposed criteria. The action is being taken in response to a request by several licensed manufacturers of Allergenic Products.

DATES: Written comments by March 8, 1979; the meeting will be held Tuesday, February 6, 1979, and interested persons may submit in writing, by January 31, 1979, topics for inclusion in the agenda of the meeting.

ADDRESSES: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65,

- 4708 -

5600 Fishers Lane, Rockville, MD 20857; the meeting will be held in Rm. 115, Bldg. 29, Bureau of Biologics, 8800 Rockville Pike, Bethesda, MD 20014; meeting agenda topics should be submitted to Steven F. Falter at the address below.

FOR FURTHER INFORMATION CONTACT: Steven F. Falter, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville

Pike, Bethesda, MD 20014, 301-443-1306.

SUPPLEMENTARY INFORMATION: In the FEDERAL REGISTER of September 26, 1978 (43 FR 43472) the Commissioner of Food and Drugs proposed to establish additional criteria for source material used in the manufacture of licensed Allergenic Products.

Interested persons were given until November 26, 1978, to submit written comments on the proposal. In response to a request by several licensed manufacturers of Allergenic Products, the Bureau of Biologics will hold a public meeting to discuss the proposed rule. Interested persons are invited to submit specific topics concerning the proposal for possible inclusion in the agenda of the meeting. In anticipation that the results of this meeting may generate additional comments to the subject document, the Commissioner is extending the comment period to March 8, 1979.

Persons planning to attend or to submit topics for the agenda should contact Steven Falter by January 31, 1979. The meeting will begin at 9 a.m. on February 6, 1979, in Rm. 115, Bldg. 29, Bureau of Biologics, 8800 Rockville Pike, Bethesda, MD 20014.

Therefore, under the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)) and under authority delegated to him (21 CFR 5.1), the Commissioner extends the comment period on the proposed additional criteria for source material of Allergenic Products to March 8, 1979.

Interested persons may, on or before March 8, 1979, submit to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, written comments regarding this proposal. Four copies of all comments shall be submitted, except that individuals may submit single copies of comments, and shall be identified with the Hearing Clerk docket number found in brackets in the heading of this document. Received comments may be seen in the above office between the hours of 9 a.m. and 4 p.m., Monday through Friday.

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Part 680

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[FR Doc. 79-2408 Filed 1-22-79; 8:45 am]

† 14.—Allergenic Product Multiple Dose Containers

† 14.1 Proposal—July 14, 1978

- 43 FR 30302 -

[21 CFR Part 680]

[Docket No. 78N-0172]

ALLERGENIC PRODUCTS

Proposed Limit of Maximum Volume in Multiple Dose Containers

AGENCY: Food and Drug Administration.

ACTION: Proposed Rule.

SUMMARY: This is a proposal to amend the biologics regulations to limit the permitted maximum volume contained in multiple dose containers to 30 milliliters thereby reducing the potential danger of contamination of allergenic products by limiting the available number of injectable doses in the container. The proposal would make the requirements for manufacturers of allergenic products consistent with the U.S. Pharmacopeia ("U.S.P.") regarding maximum volume

- 30303 -

of product for multiple dose containers.

DATES: Comments by September 12, 1978.

ADDRESS: Written comments to the Hearing Clerk (HFC-20), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Al Rothschild, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20014, 301-443-1306.

SUPPLEMENTARY INFORMATION: The Food and Drug Administration is conducting a continuing review of the regulations governing biological prod-

ucts to ensure that the criteria of safety, purity, potency, and effectiveness established by the regulations are consistent with the judgment of the scientific community. The Commissioner of Food and Drugs notes that the biological regulations are not consistent with the "U.S.P." with respect to the maximum volume of product for multiple dose containers. A multiple dose container is a container with a volume of product intended for more than one injection. "U.S.P." XIX provides that multiple dose containers should not contain "a volume of injection more than sufficient to permit the withdrawal of 30 ml." Presently, there is no such requirement in the biologics regulations. Licensed injectable allergenic products are the only biological products which are marketed in multiple dose containers with more than 30 ml of product.

Whenever a closed container is entered, there is a chance of introducing, and contaminating the product with environmental contaminants (microorganisms, foreign material, etc.) which may adversely affect the safety and effectiveness of the product. Because the volume in a multiple dose container is intended for more than one injection, special precautions must be taken each time the container is entered to preclude the introduction of environmental contaminants. Obviously, the more often the container is entered, the greater the risks. A limitation on product volume will therefore reduce the possibility of contamination.

Accordingly, the Commissioner proposes to amend the biologics regulations to require that a multiple dose container for an allergenic product shall contain no more than a volume sufficient to permit the withdrawal of 30 ml.

The Commissioner has carefully considered the environmental effects of the proposed regulations and, because the proposed action will not significantly affect the quality of the human environment, has concluded that an environmental impact statement is not required. A copy of the environmental impact assessment is on file in the office of the Hearing Clerk.

Therefore, under the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)) and under authority delegated to the Commissioner (21 CFR 5.1), it is proposed that Part 680 be amended in § 680.2, by adding new paragraph (e) to read as follows:

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§ 680.2

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[FR Doc. 78-19138 Filed 7-13-78; 8:45 am]

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†16.—Antigen E Potency Test

†16.1 **Proposal—August 3, 1979**

- 44 FR 45642 -

[21 CFR Part 680]

[Docket No. 79N-0097]

Allergenic Products; Antigen E Potency Test

AGENCY: Food and Drug Administration.

ACTION: Proposed Rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the biologics regulations concerning Allergenic Products to require potency, labeling, and lot-by-lot release standards for short ragweed pollen extracts and extracts prepared from equal parts of giant and short ragweed pollen. The proposed amendments would provide a more precise and reliable potency test for these products.

DATE: Comments by October 2, 1979.

ADDRESS: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Michael L. Hooton, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20205, 301-443-1306.

SUPPLEMENTARY INFORMATION: Allergenic Products (extracts), which have been licensed since the early 1900's, are administered to humans for the diagnosis, prevention, or treat-

ment of allergies. Current licenses for allergenic extracts prepared from short ragweed pollen require that the potency of the extract be expressed on the label as either a simple ratio of raw source material to volume of extracting fluid (e.g., 1 gram (g) of pollen extracted in 10 milliliters (mL) of extracting fluid would be labeled as a 1:10 extract) or the protein nitrogen units (PNU) of the extracts. A more precise and reliable potency test is now available for measuring allergenic extracts prepared from short ragweed pollen.

Antigen E is the major component in short ragweed pollen. Data from published studies demonstrate the importance of antigen E for the treatment of individuals sensitive to such pollen. Antigen E has been demonstrated to liberate histamine from the peripheral leukocytes of ragweed pollen sensitive individuals, initiating an allergenic reaction (see Refs. 3 through 6). In addition, the potency of allergenic extracts prepared from short ragweed pollen correlate with the antigen E values present in the extracts when measured by reactions of skin tests in allergenic human subjects (see Ref. 2). Accordingly, antigen E is demonstrated to be effective for the immunotherapy of ragweed pollen sensitive individuals and as an indicator to identify such individuals. The antigen E content of commercially prepared short ragweed pollen extracts currently varies significantly (Ref. 1), and the required potency tests do not relate to the antigen E values in the extracts. Consequently, the existing potency test based on the ratio of raw source material to volume of extracting fluid or the PNU of the extracts should be changed to a test based on the antigen E content of the extracts.

The effectiveness of a radialimmunodiffusion test to measure the antigen E content of short ragweed pollen extracts is established as a reproducible assay procedure. On October 6, 1970, the assay procedure was distributed by the Division of Biologics Standards (DBS, subsequently the Bureau of Biologics) to all manufacturers of allergenic extracts. The procedure was also discussed with the Pharmaceutical Manufacturers' Association (PMA) in December 1970. The assay procedure was demonstrated and discussed in detail with manufacturers at a workshop held on February 9, 1971. On March 16, 1971, a memorandum was sent by DBS to manufacturers requesting that they submit samples of extracts and the results of their antigen E assays for comparative assay. A second letter was sent on June 15, 1971, to those manufacturers who had not submitted samples with test results, giving them a second opportunity to do so. The results of the collaborative study, demonstrating the reliability and accuracy of the radialimmunodiffusion test for measuring the antigen E content in short ragweed pollen extracts, were distributed to each manufacturer on August 27, 1971. Since then, a number of manufacturers and potential manufacturers have received copies of the assay procedure and samples of the proposed U.S. Reference preparations.

On the basis of the published data and the results of studies performed by the Bureau of Biologics and manufacturers, FDA is proposing to amend the biologics regulations in Part 680 (21 CFR Part 680) by adding a new § 680.4 to Subpart A to require potency, labeling, and lot-by-lot release standards for short ragweed pollen extracts and extracts prepared from equal parts of giant and short ragweed pollen. The potency will be based on the quantity (units/mL) of antigen E present in those extracts compared to a standard preparation with a known quantity of antigen E.

Proposed § 680.4(a) would require the performance of, and detail the procedure for, the radialimmunodiffusion potency test for direct measurement of the antigen E content of each lot of short ragweed pollen extract or extract prepared from equal parts of giant and short ragweed pollen. Under proposed § 680.4(a)(6), an alternative test may be used if it is based on an immunological or physicalchemical test that directly or indirectly measures antigen E and can be demonstrated to give equivalent results. Based on the analysis of many lots of extracts by the Bureau of Biologics, the minimum concentration of antigen E required will be 135 units/mL (1 unit is

equal to approximately 1 microgram) for a 1:10 extract.

Proposed § 680.4(b)(1) would require that information on final container and package labels include the antigen E content in addition to either the dry weight of pollen to volume of extracting fluid or PNU value. Because the antigen E will deteriorate if extracts are warmed, proposed § 680.4(b)(2) would require that the package insert recommend storage at 2° to 8° C at all times, even when the product is being used. The proposed potency test may not be sensitive enough to test very dilute extracts for antigen E. Accordingly, the package insert would require a statement that the antigen E content of these dilute extracts is obtained by calculation from the antigen

E content of a more concentrated extract. The more concentrated extract must have been assayed for antigen E and officially released by the Director, Bureau of Biologics.

To ensure the presence of a required minimum quantity of antigen E in each lot of extract, proposed § 680.4(c) would require that manufacturers submit to the Director, Bureau of Biologics, samples of each manufactured lot of extract for FDA testing and a protocol consisting of a summary of the history of the manufacture and testing of the lot. The protocol should include at least the test results for antigen E, safety, sterility, preservative, and, when applicable, residual moisture, vacuum, and PNU. In addition, manufacturers must obtain from the Director of the Bureau an official release for each lot of extract before marketing the lot. Lot-by-lot release procedures are authorized by §§ 610.1 and 610.2 (21 CFR 610.1 and 610.2).

FDA believes that this proposed amendment to the regulations will (1) create greater uniformity in the antigen E potency of available extracts because a minimum quantity of antigen E would be required; (2) reduce or eliminate systemic reactions because the labeled potency will inform the physicians of the reactivity to be anticipated; and (3) permit effective cost control because the price of an extract can be related to the purchase of a known quantity of allergen.

The minimum dating period currently provided for Allergenic Extracts under § 610.53(a) (21 CFR 610.53(a)) will not apply to extracts prepared from short ragweed pollen once the rules proposed in this document become effective. A new dating period for each manufacturer's product will be determined by FDA as a result of appropriate license amendments supported by data from stability studies performed by manufacturers on the antigen E content of their extracts. FDA advises manufacturers of short ragweed extract that stability studies must be performed on at least two lots of such extract. Manufacturers of extracts prepared from equal parts of giant and short ragweed pollen must perform stability studies on at least two lots of such mixture. The protocol for each stability study must be submitted to the Director, Bureau of Biologics, for approval. The results of the stability studies must be submitted at regular intervals to the Director, Bureau of Biologics, and a license amendment for a dating period must be submitted by each manufacturer based on its own studies.

To permit manufacturers a reasonable period of time to solve any technical problems that they may have in performing the potency test for antigen E, and to obtain an approved license amendment for a dating period and revised labeling for their products, the effective date for these rules will be 180 days after the date of publication in the FEDERAL REGISTER of the final regulation based on this proposal. The final regulation will apply to each filling of each lot of short ragweed pollen extract, or extract prepared from equal parts of giant and short ragweed pollen, that is in the manufacturer's possession on or after the effective date. Manufacturers will be permitted to continue to prepare other mixtures of extracts of giant and short ragweed pollen, in addition to those prepared from equal parts, provided that the lot of short ragweed pollen extract used in such mixtures has been officially released by the Director, Bureau of Biologics, and the final mixed product includes appropriate antigen E labeling.

The background data, information, and references on which the agency relies in this proposal may be seen in the office of the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, between 9 a.m. and 4 p.m., Monday through Friday.

References

(1) Baer, H., H. Godfrey, C. J. Maloney, P. S. Norman, and L. M. Lichtenstein, "The Potency and Antigen E Content of Commercially Prepared Ragweed Extracts," *Journal of Allergy*, 45:347, 1970.

(2) Gleich, G. J., J. B. Larson, R. T. Jones, and H. Baer, "Measurement of the Potency of Allergy Extracts by Their Inhibitory Capacities in the Radioallergosorbent Test," *Journal of Allergy and Clinical Immunology*, 53:158, 1974.

(3) Norman, P. S. and L. M. Lichtenstein, "Capacity of Purified Antigens and Whole Pollen Extracts to Release Histamine from Leukocytes of Hayfever Patients," *Journal of Allergy and Clinical Immunology*, 52:94, 1973.

(4) Norman, P. S., L. M. Lichtenstein, and K. Ishizaka, "Diagnostic Tests in Ragweed Hayfever," *Journal of Allergy and Clinical Immunology*, 52:210, 1973.

(5) Norman, P. S., W. L. Winkenwerder, and L. M. Lichtenstein, "Immunotherapy of Hayfever with Ragweed Antigen E: Comparisons with Whole Pollen Extract in Placebo," *Journal of Allergy*, 42:93, 1968.

(6) Reisman, R. E., K. Wicher, and C. E. Arbesman, "Immunotherapy with Antigen E." *Journal of Allergy*, 44:83, 1969.

FDA has carefully considered the environmental effects of the proposed regulation and, because the proposed action will not significantly affect the quality of the human environment, has concluded that an environmental impact statement is not required. A copy of the environmental impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 502, 701, 52 Stat. 1050-1051 as amended, 1055-1056 as amended (21 U.S.C. 352, 371)) and the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1), it is proposed that Part 680 be amended in Subpart A by adding new § 680.4 to read as follows:

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§ 680.4

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[FR Doc. 79-23951 Filed 8-2-79; 8:45 am]

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†16.2 Extension of Time for Comments—October 19, 1979

- 44 FR 60333 -

[21 CFR Part 680]

[Docket No. 79N-0207]

Allergenic Products; Antigen E Potency Test; Extension of Comment Period

AGENCY: Food and Drug Administration.

ACTION: Proposed Rule; Extension of Comment Period.

SUMMARY: The Food and Drug Administration (FDA) is extending the comment period for submitting written comments on the proposed antigen E potency test for short ragweed pollen extracts and extracts prepared from equal parts of giant and short ragweed pollen.

DATES: Written comments by November 10, 1979.

ADDRESS: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Michael L. Hooton, Bureau of Biologics (HFB-620), Food and Drug Administration, Department of Health, Education, and Welfare, 8800 Rockville Pike, Bethesda, MD 20205, 301-443-1306.

SUPPLEMENTARY INFORMATION: In the FEDERAL REGISTER of August 3, 1979 (44 FR 45642), FDA proposed a new potency test to measure the quantity of antigen E in short ragweed pollen extracts and extracts prepared from equal parts of giant and short ragweed pollen. The proposal also included labeling and lot-by-lot release standards for the extract products. Interested persons were given until Octo-

ber 2, 1979, to submit written comments on the proposal. In response to a request from the American Council of Otolaryngology, which will meet to discuss the proposal in October after the comment period has ended, FDA is extending the comment period for all interested persons to November 10, 1979.

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Part 680

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[FR Doc. 79-32090 Filed 10-15-79; 8:45 am]

REDESIGNATION TABLES

At 35 FR 13922, September 2, 1970, the Biological Products regulations under Part 73 of Title 42 of the Code of Federal Regulations were recodified and republished. At 37 FR 15993, August 9, 1972, these regulations under Title 42 were transferred to the newly established Part 273 of Chapter I of Title 21 of the Code of Federal Regulations.

At 38 FR 32048, November 20, 1973, Part 273 was transferred and recodified as Subchapter F—Biologics, now comprising Parts 600 through 680.

The following tables show the relationship of the CFR section numbers under 42 CFR Part 73 and 21 CFR Part 273 to the new Subchapter F—Biologics designations (Table 1), and the relationship of the current CFR section numbers under Subchapter F to the former designations (Table 2).

Redesignation Table No. 1

Old Section	New Section	Old Section	New Section	Preamble Compilation Designation
42 CFR (1970)	42 CFR (1971)	21 CFR	21 CFR	
73.1	73.101	273.101	600.3	I.A.50, I.B.20, I.C.15, I.C.50
73.2	73.200	273.200	601.1	I.C.50, IX.D.40
73.3	73.201	273.201	601.2	I.C.50
73.4	73.202	273.202	601.10	I.C.50
73.5	73.203	273.203	601.20	I.C.50
73.6	73.204	273.204	601.3	I.C.50
73.7	73.210	273.210	601.6	I.A.50, V.15
73.9	73.230	273.230	601.4	I.B.20, I.C.50
73.15	73.236	273.236	601.44	I.C.50
NA	NA	273.237	601.11	III.B.3
73.16	73.240	273.240	601.22	I.B.20
NA	NA	273.245	601.25	I.E.3, VIII.A.5, XII.B.5
73.20	73.300	273.300	601.30	V.15
73.21	73.301	273.301	601.31	I.A.50
73.23	73.303	273.303	601.33	I.A.50
73.32	73.402	273.402	600.22	I.B.20
73.35	73.500	273.500	600.10	I.B.20
73.36	73.501	273.501	600.11	I.A.50, I.B.20, I.C.54, IX.A.5, IX.D.60
73.37	73.502	273.502	600.12	I.B.20
73.38	73.503	273.503	600.13	I.A.50, I.B.15, I.B.20, IX.A.5, X.B.41, X.D.10, X.D.15, X.D.30, X.D.35
73.39	73.504	273.504	600.14	I.A.50
73.40	73.505	273.505	600.15	I.B.30, I.B.32, I.B.35, X.D.10, X.D.15, X.D.20, X.D.30, X.D.35
73.50	73.600	273.600	610.50	I.A.50, IX.D.5
73.51	73.601	273.601	610.61	I.A.50, X.B.41
73.52	73.602	273.602	610.62	I.A.50
73.53	73.603	273.603	610.63	I.A.50, I.B.20
73.54	73.604	273.604	610.64	I.A.50
73.55	73.605	273.605	610.65	IX.D.5
73.70	73.700	273.700	610.1	I.B.20, I.C.15, I.C.50, IX.D.5
73.71	73.710	273.710	610.10	I.A.50, I.C.50
73.72	73.720	273.720	610.11	I.B.20, I.C.40
73.73	73.730	273.730	610.12	I.A.50, I.C.50, I.C.52, I.C.54, I.C.57, X.B.65, X.B.75, X.D.10, X.D.15, X.D.30, X.D.35
73.74	73.740	273.740	610.13	I.C.15, I.C.20, IX.A.5, IX.A.10, IX.D.28, IX.D.55, X.B.42, X.D.10, X.D.30, X.D.35, XII.B.5
73.74a	73.750	273.750	610.30	IX.D.45
NA	73.755	273.755	610.40	X.B.41
NA	73.756	273.756	610.41	X.B.41
73.75	73.760	273.760	610.14	I.B.20, I.C.50
73.76	73.770	273.770	610.2	I.B.20
73.77	73.780	273.780	610.18	I.B.20
73.78	73.790	273.790	610.15	I.A.50, IX.D.5
73.80	73.810	273.810	610.17	I.B.15
73.81	73.820	273.820	610.20	I.A.50, I.B.15, VIII.D.10, VIII.D.20, IX.A.5
73.82	73.830	273.830	610.21	I.A.50, VIII.D.10, VIII.D.20, VIII.D.30, X.D.10
73.83	73.840	273.840	610.50	I.A.50, I.B.15, I.B.18, I.B.20, X.D.40
73.84	73.850	273.850	610.51	I.A.50, I.B.18
73.85	73.860	273.860	610.52	I.A.50, I.B.15

Redesignation Table No. 1—Continued

Old Section	New Section	Old Section	New Section	Preamble Compilation Designation
42 CFR (1970)	42 CFR (1971)	21 CFR	21 CFR	
73.86	73.870	273.870	610.53	I.B.15, I.B.45, VIII.D.5, VIII.D.20, IX.D.35, IX.D.55, X.B.5, X.B.10, X.B.41, X.B.42, X.B.43, X.B.50, X.B.65, X.B.75, X.C.15, X.D.10, X.D.15, X.D.20, X.D.30, X.D.35, XI.B.40
73.94	73.9024	273.9024	680.14	I.B.20
73.100	73.1000	273.1000	630.1	I.A.50, IX.D.40, IX.D.45
73.101	73.1001	273.1001	630.2	I.A.50, IX.D.40, IX.D.45
73.102	73.1002	273.1002	630.4	I.A.50, I.B.20, IX.D.5, IX.D.40, IX.D.45
73.103	73.1003	273.1003	630.3	IX.D.40, IX.D.45
73.104	73.1004	273.1004	630.5	I.A.50, I.B.15, I.B.20, IX.D.40, IX.D.45
73.105	73.1005	273.1005	630.6	I.B.20, IX.D.5, IX.D.40, IX.D.45
73.110	73.1020	273.1020	630.10	I.A.50, IX.A.10, IX.D.5, IX.D.45
73.111	73.1021	273.1021	630.14	IX.D.5, IX.D.45
73.112	73.1022	273.1022	630.12	I.A.50, IX.D.5, IX.D.45
73.113	73.1023	273.1023	630.13	IX.D.5, IX.D.45
73.114	73.1024	273.1024	630.16	I.B.20, IX.A.10, IX.B.50, IX.D.5, IX.D.45
73.115	73.1025	273.1025	630.15	IX.D.5, IX.D.45
73.116	73.1026	273.1026	630.17	I.A.50, I.B.15, IX.A.5, IX.D.45
73.117	73.1027	273.1027	630.11	IX.D.45
73.118	73.1028	273.1028	630.18	IX.D.45
73.130	73.1040	273.1040	630.20	IX.D.5
73.131	73.1041	273.1041	630.22	IX.D.5
73.132	73.1042	273.1042	630.23	I.A.50, IX.D.5, IX.D.40
73.133	73.1043	273.1043	630.24	IX.D.5
73.134	73.1044	273.1044	630.21	I.B.15, IX.D.5
73.135	73.1045	273.1045	630.25	IX.D.5
73.140	73.1060	273.1060	630.30	IX.A.5, IX.A.10, IX.B.10, IX.B.40, IX.D.25
73.141	73.1061	273.1061	630.32	IX.B.10, IX.D.25
73.142	73.1062	273.1062	630.35	IX.B.10, IX.B.25, IX.B.40, IX.D.25, IX.D.45
73.143	73.1063	273.1063	630.34	IX.D.25
73.144	73.1064	273.1064	630.36	I.A.50, I.B.25, IX.A.5
73.145	73.1065	273.1065	630.31	IX.D.25
73.146	73.1066	273.1066	630.37	IX.D.25
73.151	73.1081	273.1081	630.42	I.A.50
73.152	73.1082	273.1082	630.43	IX.D.45
73.154	73.1084	273.1084	630.41	I.A.50
73.160	73.1100	273.1100	630.50	IX.A.10, IX.B.40, IX.D.35
73.161	73.1101	273.1101	630.52	IX.D.35
73.162	73.1102	273.1102	630.55	IX.B.40, IX.D.35
73.163	73.1103	273.1103	630.54	IX.D.35
73.164	73.1104	273.1104	630.56	I.A.50, I.B.25, IX.D.35
73.165	73.1105	273.1105	630.51	IX.D.35
73.166	73.1106	273.1106	630.57	IX.D.35
73.170	73.1140	273.1140	630.70	IX.B.65, IX.D.60
73.171	73.1141	273.1141	630.72	IX.D.60
73.172	73.1142	273.1142	630.71	IX.D.60
73.173	73.1143	273.1143	630.74	I.C.57, IX.B.65, IX.D.60
73.174	73.1144	273.1144	630.73	IX.B.65, IX.D.60
73.175	73.1145	273.1145	630.75	IX.D.60, X.D.40
73.176	73.1146	273.1146	630.76	IX.D.60
73.190	73.1120	273.1120	630.60	IX.A.10, IX.B.10, IX.B.40, IX.D.55
73.191	73.1121	273.1121	630.62	IX.B.10, IX.D.55
73.192	73.1122	273.1122	630.65	IX.B.10, IX.B.40, IX.B.45, IX.D.55

Redesignation Table No. 1—Continued

Old Section	New Section	Old Section	New Section	Preamble Compilation Designation
42 CFR (1970)	42 CFR (1971)	21 CFR	21 CFR	
73.193	73.1123	273.1123	630.64	IX.D.55
73.194	73.1124	273.1124	630.66	I.A.50, I.B.25, IX.D.55, X.D.40
73.195	73.1125	273.1125	630.61	IX.D.55
73.196	73.1126	273.1126	630.67	IX.D.55
NA	73.1160	273.1160	630.80	IX.D.28
NA	73.1161	273.1161	630.82	IX.D.28
NA	73.1162	273.1162	630.85	IX.D.28
NA	73.1163	273.1163	630.84	IX.B.65, IX.D.28
NA	73.1164	273.1164	630.86	I.A.50, IX.D.28, X.D.40
NA	73.1165	273.1165	630.81	IX.D.28
NA	73.1166	273.1166	630.87	IX.D.28
73.300	73.3000	273.3000	640.1	I.A.50, X.D.5
73.301	73.3001	273.3001	640.3	X.D.5
73.302	73.3002	273.3002	640.4	I.B.20, X.C.15, X.D.5, X.D.15, X.D.20, X.D.35
73.303	73.3003	273.3003	640.5	I.B.20, I.B.37, X.D.5
73.304	73.3004	273.3004	640.2	I.B.20, I.B.30, I.B.37, I.C.57, II.B.7, X.B.41, X.C.15, X.D.5, X.D.20
73.305	73.3005	273.3005	640.7	I.A.50, I.B.37, II.B.7, X.B.41, X.B.47, X.C.15, X.D.5, X.D.35
73.306	73.3006	273.3006	640.6	I.B.15, X.D.5
73.310	73.3040	273.3040	640.50	X.D.30
73.311	73.3041	273.3041	640.52	X.D.30
73.312	73.3042	273.3042	640.51	II.B.7, X.B.41, X.B.47, X.D.30
73.320	73.3020	273.3020	640.10	X.D.10
73.321	73.3021	273.3021	640.12	X.D.10
73.322	73.3022	273.3022	640.13	X.D.10
73.323	73.3023	273.3023	640.14	X.D.10
73.324	73.3024	273.3024	640.15	X.D.10
73.325	73.3025	273.3025	640.16	I.B.15, X.C.15, X.D.10
73.326	73.3026	273.3026	640.11	X.D.10, X.D.20
73.327	73.3027	273.3027	640.17	I.B.30, X.D.10
73.328	73.3028	273.3028	640.18	II.B.7, X.D.10
73.350	73.3520	273.3520	640.110	X.B.35, X.D.55
73.351	73.3521	273.3521	640.112	I.A.50, X.B.35, X.D.55
73.352	73.3522	273.3522	640.113	X.D.55
73.353	73.3523	273.3523	640.114	X.B.35, X.D.55
73.354	73.3524	273.3524	640.111	I.B.15, X.D.55
73.355	73.3500	273.3500	640.100	X.D.50
73.356	73.3501	273.3501	640.102	X.D.50
73.357	73.3502	273.3502	640.103	X.D.50
73.358	73.3503	273.3503	640.104	X.B.35, X.D.50
73.359	73.3504	273.3504	640.101	X.D.50
73.400	73.4000	273.4000	620.1	VIII.D.20
73.401	73.4001	273.4001	620.3	VIII.D.20
73.402	73.4002	273.4002	620.2	VIII.D.20
73.403	73.4003	273.4003	620.5	VIII.D.20
73.404	73.4004	273.4004	620.4	VIII.D.20
73.405	73.4005	273.4005	620.6	I.C.40, VIII.A.45, VIII.D.20
73.406	73.4006	273.4006	620.7	VIII.D.20
73.410	73.4020	273.4020	620.10	VIII.D.30
73.411	73.4021	273.4021	620.12	VIII.D.30
73.412	73.4022	273.4022	620.11	VIII.D.30
73.413	73.4023	273.4023	620.13	VIII.D.30
73.414	73.4024	273.4024	620.14	VIII.D.30, X.D.40
73.415	73.4025	273.4025	620.15	VIII.D.30
73.420	73.4040	273.4040	620.20	VIII.D.5
73.421	73.4041	273.4041	620.22	VIII.D.5
73.422	73.4042	273.4042	620.21	VIII.D.5
73.423	73.4043	273.4043	620.23	VIII.D.5
73.424	73.4044	273.4044	620.24	VIII.D.5, X.D.40
73.424(d)	73.4044(d)	273.4044(d)	620.25	VIII.D.5
73.500	73.9000	273.9000	680.1	XII.B.10, XII.B.12

Redesignation Table No. 1—Continued

Old Section	New Section	Old Section	New Section	Preamble Compilation Designation
42 CFR (1970)	42 CFR (1971)	21 CFR	21 CFR	
73.501	73.9001	273.9001	680.2	XII.B.10, XII.B.12, XII.B.14
73.502	73.9002	273.9002	680.3	I.C.54, I.C.87, XII.B.10
73.600	73.2000	273.2000	650.1	XI.B.20
73.601	73.2001	273.2001	650.2	XI.B.20
73.602	73.2002	273.2002	650.3	XI.B.20
73.603	73.2003	273.2003	650.4	XI.B.20
73.604	73.2004	273.2004	650.5	XI.B.20
73.605	73.2005	273.2005	650.6	X.D.40, XI.B.20
73.606	73.2006	273.2006	650.7	XI.B.20
73.610	73.2020	273.2020	650.10	XI.B.40
73.611	73.2021	273.2021	650.12	XI.B.40
73.612	73.2022	273.2022	650.13	XI.B.40, XII.B.5
73.613	73.2023	273.2023	650.14	XI.B.40, XII.B.5
73.614	73.2024	273.2024	650.11	X.D.40, XI.B.40
73.615	73.2025	273.2025	650.15	XI.B.40, XII.B.5

Redesignation Table No. 2

New Section 21 CFR	Old Section 21 CFR	New Section 42 CFR (1971)	Old Section 42 CFR (1970)	Preamble Compilation Designation
600.3	273.101	73.101	73.1	I.A.50, I.B.20, I.C.15, I.C.50
600.10	273.500	73.500	73.35	I.B.20
600.11	273.501	73.501	73.36	I.A.50, I.B.20, I.C.54, IX.A.5, IX.D.60
600.12	273.502	73.502	73.37	I.B.20
600.13	273.503	73.503	73.38	I.A.50, I.B.15, I.B.20, IX.A.5, X.B.41, X.D.10, X.D.15, X.D.30, X.D.35
600.14	273.504	73.504	73.39	I.A.50
600.15	273.505	73.505	73.40	I.B.30, I.B.32, I.B.35, X.D.10, X.D.15, X.D.20, X.D.30, X.D.35
600.22	273.402	73.402	73.32	I.B.20
601.1	273.200	73.200	73.2	I.C.50, IX.D.40
601.2	273.201	73.201	73.3	I.C.50
601.3	273.204	73.204	73.6	I.C.50
601.4	273.230	73.230	73.9	I.B.20, I.C.50
601.6	273.210	73.210	73.7	I.A.50, V.15
601.10	273.202	73.202	73.4	I.C.50
601.11	273.237	NA	NA	III.B.3
601.20	273.203	73.203	73.5	I.C.50
601.22	273.240	73.240	73.16	I.B.20
601.25	273.245	NA	NA	I.E.3, VIII.A.5, XII.B.5
601.30	273.300	73.300	73.20	V.15
601.31	273.301	73.301	73.21	I.A.50
601.33	273.303	73.303	73.23	I.A.50
601.44	273.236	73.236	73.15	I.C.50
606.3	NA	NA	NA	IV.B.3
606.20	NA	NA	NA	IV.B.3
606.40	NA	NA	NA	IV.B.3
606.60	NA	NA	NA	IV.B.3, IV.B.5
606.65	NA	NA	NA	IV.B.3
606.100	NA	NA	NA	IV.B.3
606.110	NA	NA	NA	IV.B.3
606.120	NA	NA	NA	II.B.7, IV.B.3
606.140	NA	NA	NA	IV.B.3
606.151	NA	NA	NA	IV.B.3
606.160	NA	NA	NA	IV.B.3
606.165	NA	NA	NA	IV.B.3
606.170	NA	NA	NA	IV.B.3
607.3	NA	NA	NA	III.B.3
607.7	NA	NA	NA	III.B.3
607.20	NA	NA	NA	III.B.3
607.21	NA	NA	NA	III.B.3
607.22	NA	NA	NA	III.B.3
607.25	NA	NA	NA	III.B.3
607.26	NA	NA	NA	III.B.3
607.30	NA	NA	NA	III.B.3
607.31	NA	NA	NA	III.B.3
607.35	NA	NA	NA	III.B.3
607.37	NA	NA	NA	III.B.3
607.39	NA	NA	NA	III.B.3
607.40	NA	NA	NA	III.B.3
607.65	NA	NA	NA	III.B.3
610.1	273.700	73.700	73.70	I.B.20, I.C.15, I.C.50, IX.D.5
610.2	273.770	73.770	73.76	I.B.20
610.10	273.710	73.710	73.71	I.A.50, I.C.50
610.11	273.720	73.720	73.72	I.B.20, I.C.40
610.11a	NA	NA	NA	I.C.43
610.12	273.730	73.730	73.73	I.A.50, I.C.50, I.C.52, I.C.54, I.C.57, X.B.65, X.B.75, X.D.10, X.D.15, X.D.30, X.D.35

Redesignation Table No. 2—Continued

New Section 21 CFR	Old Section 21 CFR	New Section 42 CFR (1971)	Old Section 42 CFR (1970)	Preamble Compilation Designation
610.13	273.740	73.740	73.74	I.C.15, I.C.20, IX.A.5, IX.A.10, IX.D.26, IX.D.55, X.B.42, X.D.10, X.D.30, X.D.35, XII.B.5
610.14	273.760	73.760	73.75	I.B.20, I.C.50
610.15	273.790	73.790	73.78	I.A.50, IX.D.5
610.17	273.810	73.810	73.80	I.B.15
610.18	273.780	73.780	73.77	I.B.20
610.19	NA	NA	NA	VIII.A.5
610.20	273.820	73.820	73.81	I.A.50, I.B.15, VIII.D.10, VIII.D.20, IX.A.5
610.21	273.830	73.830	73.82	I.A.50, VIII.D.10, VIII.D.20, VIII.D.30, X.D.10
610.30	273.750	73.750	73.74a	IX.D.45
610.40	273.755	73.755	NA	X.B.41
610.41	273.756	73.756	NA	X.B.41
610.42	NA	NA	NA	II.B.7
610.50	273.840	73.840	73.83	I.A.50, I.B.15, I.B.18, I.B.20, X.D.40
610.51	273.850	73.850	73.84	I.A.50, I.B.18
610.52	273.860	73.860	73.85	I.A.50, I.B.15
610.53	273.870	73.870	73.86	I.B.15, I.B.45, VIII.D.5, VIII.D.20, IX.D.35, IX.D.55, X.B.5, X.B.10, X.B.41, X.B.42, X.B.43, X.B.50, X.B.65, X.B.75, X.C.15, X.D.10, X.D.15, X.D.20, X.D.30, X.D.35, XI.B.40
610.60	273.600	73.600	73.50	I.A.50, IX.D.5
610.61	273.601	73.601	73.51	I.A.50, X.B.41
610.62	273.602	73.602	73.52	I.A.50
610.63	273.603	73.603	73.53	I.A.50, I.B.20
610.64	273.604	73.604	73.54	I.A.50
610.65	273.605	73.605	73.55	IX.D.5
620.1	273.4000	73.4000	73.400	VIII.D.20
620.2	273.4002	73.4002	73.402	VIII.D.20
620.3	273.4001	73.4001	73.401	VIII.D.20
620.4	273.4004	73.4004	73.404	VIII.D.20
620.5	273.4003	73.4003	73.403	VIII.D.20
620.6	273.4005	73.4005	73.405	I.C.40, VIII.A.45, VIII.D.20
620.7	273.4006	73.4006	73.406	VIII.D.20
620.10	273.4020	73.4020	73.410	VIII.D.30
620.11	273.4022	73.4022	73.412	VIII.D.30
620.12	273.4021	73.4021	73.411	VIII.D.30
620.13	273.4023	73.4023	73.413	VIII.D.30
620.14	273.4024	73.4024	73.414	VIII.D.30, X.D.40
620.15	273.4025	73.4025	73.415	VIII.D.30
620.20	273.4040	73.4040	73.420	VIII.D.5
620.21	273.4042	73.4042	73.422	VIII.D.5
620.22	273.4041	73.4041	73.421	VIII.D.5
620.23	273.4043	73.4043	73.423	VIII.D.5
620.24	273.4044	73.4044	73.424	VIII.D.5, X.D.40
620.25	273.4044(d)	73.4044(d)	73.424(d)	VIII.D.5
620.30	NA	NA	NA	VIII.D.10
620.31	NA	NA	NA	VIII.D.10
620.32	NA	NA	NA	VIII.D.10
620.33	NA	NA	NA	VIII.D.10
620.34	NA	NA	NA	VIII.D.10
620.35	NA	NA	NA	VIII.D.10, X.D.40
620.36	NA	NA	NA	VIII.D.10
630.1	273.1000	73.1000	73.100	I.A.50, IX.D.40, IX.D.45
630.2	273.1001	73.1001	73.101	I.A.50, IX.D.40, IX.D.45
630.3	273.1003	73.1003	73.103	IX.D.40, IX.D.45

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Redesignation Table No. 2—Continued

New Section 21 CFR	Old Section 21 CFR	New Section 42 CFR (1971)	Old Section 42 CFR (1970)	Preamble Compilation Designation
630.4	273.1002	73.1002	73.102	I.A.50, I.B.20, IX.D.5, IX.D.40, IX.D.45
630.5	273.1004	73.1004	73.104	I.A.50, I.B.15, I.B.20, IX.D.40, IX.D.45
630.6	273.1005	73.1005	73.105	I.B.20, IX.D.5, IX.D.40, IX.D.45
630.10	273.1020	73.1020	73.110	I.A.50, IX.A.10, IX.D.5, IX.D.45
630.11	273.1027	73.1027	73.117	IX.D.45
630.12	273.1022	73.1022	73.112	I.A.50, IX.D.5, IX.D.45
630.13	273.1023	73.1023	73.113	IX.D.5, IX.D.45
630.14	273.1021	73.1021	73.111	IX.D.5, IX.D.45
630.15	273.1025	73.1025	73.115	IX.D.5, IX.D.45
630.16	273.1024	73.1024	73.114	I.B.20, IX.A.10, IX.B.50, IX.D.5, IX.D.45
630.17	273.1026	73.1026	73.116	I.A.50, I.B.15, IX.A.5, IX.D.45
630.18	273.1028	73.1028	73.118	IX.D.45
630.20	273.1040	73.1040	73.120	IX.D.5
630.21	273.1044	73.1044	73.134	I.B.15, IX.D.5
630.22	273.1041	73.1041	73.131	IX.D.5
630.23	273.1042	73.1042	73.132	I.A.50, IX.D.5, IX.D.40
630.24	273.1043	73.1043	73.133	IX.D.5
630.25	273.1045	73.1045	73.135	IX.D.5
630.30	273.1060	73.1060	73.140	IX.A.5, IX.A.10, IX.B.10, IX.B.40, IX.D.25
630.31	273.1065	73.1065	73.145	IX.D.25
630.32	273.1061	73.1061	73.141	IX.B.10, IX.D.25
630.34	273.1063	73.1063	73.143	IX.D.25
630.35	273.1062	73.1062	73.142	IX.B.10, IX.B.25, IX.B.40, IX.D.25, IX.D.45
630.36	273.1064	73.1064	73.144	I.A.50, I.B.25, IX.A.5
630.37	273.1066	73.1066	73.146	IX.D.25
630.41	273.1084	73.1084	73.154	I.A.50
630.42	273.1081	73.1081	73.151	I.A.50
630.43	273.1082	73.1082	73.152	IX.D.45
630.50	273.1100	73.1100	73.160	IX.A.10, IX.B.40, IX.D.35
630.51	273.1005	73.1005	73.165	IX.D.35
630.52	273.1101	73.1101	73.161	IX.D.35
630.54	273.1103	73.1103	73.163	IX.D.35
630.55	273.1102	73.1102	73.162	IX.B.40, IX.D.35
630.56	273.1104	73.1104	73.164	I.A.50, I.B.25, IX.D.35
630.57	273.1106	73.1106	73.166	IX.D.35
630.60	273.1120	73.1120	73.190	IX.A.10, IX.B.10, IX.B.40, IX.D.55
630.61	273.1125	73.1125	73.195	IX.D.55
630.62	273.1121	73.1121	73.191	IX.B.10, IX.D.55
630.64	273.1123	73.1123	73.193	IX.D.55
630.65	273.1122	73.1122	73.192	IX.B.10, IX.B.40, IX.B.45, IX.D.55
630.66	273.1124	73.1124	73.194	I.A.50, I.B.25, IX.D.55, X.D.40
630.67	273.1126	73.1126	73.196	IX.D.55
630.70	273.1140	73.1140	73.170	IX.B.65, IX.D.60
630.71	273.1142	73.1142	73.172	IX.D.60
630.72	273.1141	73.1141	73.171	IX.D.60
630.73	273.1144	73.1144	73.174	IX.B.65, IX.D.60
630.74	273.1143	73.1143	73.173	I.C.57, IX.B.65, IX.D.60
630.75	273.1145	73.1145	73.175	IX.D.60, X.D.40
630.76	273.1146	73.1146	73.176	IX.D.60
630.80	273.1160	73.1160	NA	IX.D.28
630.81	273.1165	73.1165	NA	IX.D.28
630.82	273.1161	73.1161	NA	IX.D.28
630.84	273.1163	73.1163	NA	IX.B.65, IX.D.29
630.85	273.1162	73.1162	NA	IX.D.28
630.86	273.1164	73.1164	NA	I.A.50, IX.D.28, X.D.40
630.87	273.1166	73.1166	NA	IX.D.28
630.90	NA	NA	NA	IX.D.10
630.91	NA	NA	NA	IX.D.10

Redesignation Table No. 2—Continued

New Section 21 CFR	Old Section 21 CFR	New Section 42 CFR (1971)	Old Section 42 CFR (1970)	Preamble Compilation Designation
630.92	NA	NA	NA	IX.D.10
630.93	NA	NA	NA	IX.D.10
630.94	NA	NA	NA	IX.D.10
630.95	NA	NA	NA	IX.D.10
630.96	NA	NA	NA	IX.D.10
630.97	NA	NA	NA	IX.D.10
640.1	273.3000	73.3000	73.300	I.A.50, X.D.50
640.2	273.3004	73.3004	73.304	I.B.20, I.B.30, I.B.37, I.C.57, II.B.7, X.B.41, X.C.15, X.D.5, X.D.20
640.3	273.3001	73.3001	73.301	X.D.5
640.4	273.3002	73.3002	73.302	I.B.20, X.C.15, X.D.5, X.D.15, X.D.20, X.D.35
640.5	273.3003	73.3003	73.303	I.B.20, I.B.37, X.D.5
640.6	273.3006	73.3006	73.306	I.B.15, X.D.5
640.7	273.3005	73.3005	73.305	I.A.50, I.B.37, II.B.7, X.B.41, X.B.47, X.C.15, X.D.5, X.D.35
640.10	273.3020	73.3020	73.320	X.D.10
640.11	273.3026	73.3026	73.326	X.D.10, X.D.20
640.12	273.3021	73.3021	73.321	X.D.10
640.13	273.3022	73.3022	73.322	X.D.10
640.14	273.3023	73.3023	73.323	X.D.10
640.15	273.3024	73.3024	73.324	X.D.10
640.16	273.3025	73.3025	73.325	I.B.15, X.C.15, X.D.10
640.17	273.3027	73.3027	73.327	I.B.30, X.D.10
640.18	273.3029	73.3029	73.329	II.B.7, X.D.10
640.20	NA	NA	NA	X.D.15
640.21	NA	NA	NA	X.D.15
640.22	NA	NA	NA	X.C.15, X.D.15
640.23	NA	NA	NA	X.D.15
640.24	NA	NA	NA	X.D.15, X.D.20
640.25	NA	NA	NA	X.D.15, X.D.20
640.26	NA	NA	NA	II.B.7, X.B.41, X.B.47, X.D.15
640.27	NA	NA	NA	IV.B.3, X.D.15
640.28	NA	NA	NA	X.D.15
640.30	NA	NA	NA	X.D.20
640.31	NA	NA	NA	X.D.20
640.32	NA	NA	NA	X.C.15, X.D.20
640.33	NA	NA	NA	X.D.20
640.34	NA	NA	NA	X.C.15, X.D.20
640.35	NA	NA	NA	II.B.7, X.D.20
640.36	NA	NA	NA	X.D.20
640.50	273.3040	73.3040	73.310	X.D.30
640.51	273.3042	73.3042	73.312	II.B.7, X.B.41, X.B.47, X.D.30
640.52	273.3041	73.3041	73.311	X.D.30
640.53	NA	NA	NA	X.D.30
640.54	NA	NA	NA	X.D.30
640.55	NA	NA	NA	X.D.30
640.56	NA	NA	NA	X.D.30
640.57	NA	NA	NA	X.D.30
640.60	273.3100	NA	NA	X.D.35
640.61	273.3101	NA	NA	X.D.35
640.62	273.3102	NA	NA	X.D.35
640.63	273.3103	NA	NA	X.D.35
640.64	273.3104	NA	NA	X.D.35
640.65	273.3105	NA	NA	X.D.35
640.66	273.3106	NA	NA	X.D.35
640.67	273.3107	NA	NA	X.B.41, X.D.35
640.68	273.3108	NA	NA	X.D.35
640.69	273.3109	NA	NA	X.B.41, X.D.35
640.70	273.3110	NA	NA	X.B.47, X.D.35
640.71	NA	NA	NA	X.D.35
640.72	NA	NA	NA	X.D.35
640.73	NA	NA	NA	X.D.35
640.74	NA	NA	NA	X.D.35
640.75	NA	NA	NA	X.D.35

Redesignation Table No. 2—Continued

New Section 21 CFR	Old Section 21 CFR	New Section 42 CFR (1971)	Old Section 42 CFR (1970)	Preamble Compilation Designation
640.78	NA	NA	NA	X.D.35
640.80	NA	NA	NA	X.D.40
640.81	NA	NA	NA	X.D.40
640.82	NA	NA	NA	X.D.40
640.83	NA	NA	NA	X.D.40
640.84	NA	NA	NA	X.D.40
640.85	NA	NA	NA	X.D.40
640.86	NA	NA	NA	X.D.40
640.90	NA	NA	NA	X.D.40
640.91	NA	NA	NA	X.D.40
640.92	NA	NA	NA	X.D.40
640.93	NA	NA	NA	X.D.40
640.94	NA	NA	NA	X.D.40
640.95	NA	NA	NA	X.D.40
640.96	NA	NA	NA	X.D.40
640.100	273.3500	73.3500	73.355	X.D.50
640.101	273.3504	73.3504	73.359	X.D.50
640.102	273.3501	73.3501	73.356	X.D.50
640.103	273.3502	73.3502	73.357	X.D.50
640.104	273.3503	73.3503	73.358	X.B.35, X.D.50
640.110	273.3520	73.3520	73.350	X.B.35, X.D.5[4]
640.111	273.3524	73.3524	73.354	I.B.15, X.D.55
640.112	273.3521	73.3521	73.351	I.A.50, X.B.35, X.D.55
640.113	273.3522	73.3522	73.352	X.D.55
640.114	273.3523	73.3523	73.353	X.B.35, X.D.55
650.1	273.2000	73.2000	73.600	XI.B.20
650.2	273.2001	73.2001	73.601	XI.B.20
650.3	273.2002	73.2002	73.602	XI.B.20
650.4	273.2003	73.2003	73.603	XI.B.20
650.5	273.2004	73.2004	73.604	XI.B.20
650.6	273.2005	73.2005	73.605	X.D.40, XI.B.20
650.7	273.2006	73.2006	73.606	XI.B.20
650.10	273.2020	73.2020	73.610	XI.B.40
650.11	273.2024	73.2024	73.614	X.D.40, XI.B.40
650.12	273.2021	73.2021	73.611	XI.B.40
650.13	273.2022	73.2022	73.612	XI.B.40, XII.B.5
650.14	273.2023	73.2023	73.613	XI.B.40, XII.B.5
650.15	273.2025	73.2025	74.615	XI.B.40, XII.B.5
650.16	NA	NA	NA	XII.B.5
660.1	273.5000	NA	NA	X.B.41, X.B.42, X.D.40
660.2	273.5004	NA	NA	X.B.41, X.B.42, X.B.43
660.3	273.5001	NA	NA	X.B.41, X.B.42
660.4	273.5002	NA	NA	X.B.41, X.B.42
660.5	273.5003	NA	NA	X.B.41, X.B.42
660.6	NA	NA	NA	X.B.43
660.10	273.5100	NA	NA	X.B.65
660.11	273.5101	NA	NA	X.B.65
660.12	273.5102	NA	NA	X.B.65
660.13	273.5103	NA	NA	X.B.65
660.14	273.5104	NA	NA	X.B.65
660.15	273.5105	NA	NA	X.B.65, X.D.40
660.20	NA	NA	NA	X.B.5
660.21	NA	NA	NA	X.B.5
660.22	NA	NA	NA	X.B.5
660.23	NA	NA	NA	X.B.5
660.24	NA	NA	NA	X.B.5
660.25	NA	NA	NA	X.B.5
660.26	NA	NA	NA	X.B.5
660.27	NA	NA	NA	X.B.5
660.28	NA	NA	NA	X.B.5
660.29	NA	NA	NA	X.B.5
660.30	NA	NA	NA	X.B.75
660.31	NA	NA	NA	X.B.75
660.32	NA	NA	NA	X.B.75
660.33	NA	NA	NA	X.B.75
660.34	NA	NA	NA	X.B.75
660.35	NA	NA	NA	X.B.75
660.36	NA	NA	NA	X.B.75
660.40	NA	NA	NA	X.B.43

Redesignation Table No. 2—Continued

New Section 21 CFR	Old Section 21 CFR	New Section 42 CFR (1971)	Old Section 42 CFR (1970)	Preamble Compilation Designation
660.41	NA	NA	NA	X.B.43
660.42	NA	NA	NA	X.B.43
660.43	NA	NA	NA	X.B.43
660.44	NA	NA	NA	X.B.43
660.45	NA	NA	NA	X.B.43
660.46	NA	NA	NA	X.B.43
680.1	273.9000	73.9000	73.500	XII.B.10, XII.B.12
680.2	273.9001	73.9001	73.501	XII.B.10, XII.B.12, XII.B.14
680.3	273.9002	73.9002	73.502	I.C.54, I.C.57, XII.B.10
680.4	NA	NA	NA	XII.B.16
680.14	273.9024	73.9024	73.94	I.B.20
680.20	NA	NA	NA	X.B.10
680.21	NA	NA	NA	X.B.10
680.22	NA	NA	NA	X.B.10
680.23	NA	NA	NA	X.B.10
680.24	NA	NA	NA	X.B.10
680.25	NA	NA	NA	X.B.10
680.26	NA	NA	NA	X.B.10
(Proposal)	273.5020	NA	NA	X.B.50
(Proposal)	273.5021	NA	NA	X.B.50
(Proposal)	273.5022	NA	NA	X.B.50
(Proposal)	273.5023	NA	NA	X.B.50
(Proposal)	273.5024	NA	NA	X.B.50

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